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The Jackson Lecture.[1]

HISTORY, HYPOTHESIS, AND THE HEART.

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TONIGHT we honour the memory of Ernest Sandford Jackson and acknowledge again our debt to him and to our colleagues of his generation. Acknowledgement of such a debt does not, of course, constitute repayment, which must be made in kind, but it helps to induce a wholesome frame of mind in the indebted.

As doctors we accept, in the business of making our livings or our fortunes, certain legal and ethical obligations over and above those of the average citizen. Beyond those which apply to us all there are also certain other duties to the community for the performance of which, since they are possible only to men of exceptional gifts, we have to thank men like Ernest Jackson.

These matters concern chiefly the long-range planning for the development of the profession in its relation to the community in the years ahead, and assessment of the needs and perils involved. These require wisdom, ability to lead one's profession and the community, and a great deal of determination and industry. They also demand the internal whip of an acute sense of public responsibility, a sort of unguilty conscience concerning future generations. They also require what I would call a sense of history. Dr. Jackson was fortunately possessed of these gifts. In the development of the Brisbane General Hospital and its school of nursing, of the British Medical Association in Queensland, and of this medical school, his wisdom and work are embodied. His memorial is about us to be seen.

By the term "sense of history" I mean something more easily exemplified than defined. Essentially perhaps it is a perception of the unity of the future and the past and a realization of fellowship with one's predecessors and successors. Santayana, the poet and philosopher, defined it in his "Testament":

> Spared by the Furies, for the Fates were kind,
> I paced the pillared cloisters of the mind,
> All times my present, everywhere my place.

I would like to suggest to you that the attitude of mind or state of enlightenment, expressed in this last line, is as necessary technically to us in our medical science and art as it is to the poet and philosopher. To the drudgery of medical studies it offers the twofold solace that the knowledge and skill we labour to acquire have been amassed for us by our masters in the past over many

[1] Delivered at a meeting of the Queensland Branch of the British Medical Association on November 7, 1952.

hundreds of years; and next, that we are as yet still ignorant—that there are enormous discoveries yet to be made, the clue to which, if we could only see, lies in even the most pedestrian piece of clinical work.

Such a sense of history is essential to the work of such men as Jackson, and the decision that the Jackson lecture should be of an historical nature was made, I believe, partly on account of Dr. Jackson's interest in things historical, and partly because there is no part of our medical knowledge so highly respected and so shockingly neglected. An historical sense I take to be an essential part of the discipline of the scientific mind, and those who teach should particularly be able to inculcate the historical perspective into the habits of thought of those with whose education they are entrusted.

Lectures on history should be delivered only by an historian. We do not permit enthusiastic amateurs to teach cardiology or gynæcology, and history is a more complex subject than either. But history, like for instance mathematics, has a permeating and inescapable influence in all branches of human learning. We do not hesitate to apply mathematics to medicine because we are not mathematicians. In fact, we fail to apply it often enough since most doctors are such poor mathematicians as not to see where the mathematician should be called in to help with our problems.

In coronary occlusion, for instance, the role of hæmorrhage into an atheromatous plaque has been canvassed for many years. Paterson (1936), Wartman (1938), Winternitz (1938) and Horn and Finkelstein (1940) have found evidence to support the idea that such hæmorrhage might precipitate coronary arterial blockage. Professor E. S. J. King has, however, pointed out the mathematical difficulties. In simplified form they are that the blood supply to the wall of the artery comes from the lumen, and for such hæmorrhage to occur the pressure in the lumen must be less than the capillary or arteriolar pressure within the vessel wall. Since then the pressure in the lumen is related in inverse fashion to the area of the lumen at any point, and to the velocity of the blood-stream at that point, it would seem likely that hæmorrhage into an atheromatous plaque may occur only where the lumen is, to all physiological intents and purposes, already so narrowed as to be practically occluded.

As with mathematics, so with history. Few of us are sufficiently apt historians to know when and how historical science is applicable in our own particular study. One remedy would be that physicians should have mathematical and historical colleagues, that all should be sufficiently informed in each other's subject to discuss mutual problems profitably, and that there should be ample and ready opportunity to do so. This is, of course, one definition of a university.

We are told sometimes that medicine is ceasing to be a university subject, that we are becoming isolated, geographically and intellectually, from university membership. If this is so, then we must realize that our thinking and teaching are in grave danger of degeneration. I will not comment further except to point out that Dr. Ian Mackerras has recently expressed his concern that medical education of today seemed to him to be failing badly to impose scientific discipline on the thinking of students and graduates.

We can, of course, read history and mathematics. Books, however, must be used sensibly, and I doubt whether we do so use them. Good text-books should, for instance, utterly and entirely dispense with the need for the formal academic lecture; but our practice ignores this aspect. Other books and monographs expound the work and ideas of their various authors. But these, however excellent, cannot replace informal discussion of the type mentioned. The book is a one-sided discussion, the author can only guess at the doubts and difficulties of the reader, the latter must interpret as best he may any seeming ambiguities or contradictions in his author.

To become an historian from books alone is as practicable as becoming a physician by the same method. History and medicine have indeed much in common. History is at once a science and an art and, as in medicine, historians are divided as to which is the more important aspect. Perhaps the older historians tend to be scientific and the older doctors humanistic.

Professor Bury, who was Trevelyan's predecessor in the Chair of History at Cambridge, took the view, Trevelyan reminds us, that "history is a science, no more and no less". However, Trevelyan continues:

> But as a rash young man I ventured to contravert his definition of history. . . . I argued that it was both a science and an art: that the discovery of historical facts should be scientific in method, but that the exposition of them partook of an art, the art of written words commonly called literature. More than forty years have passed and I hold the same opinion still as to the dual nature of history.

Elsewhere Trevelyan enlarged on his own viewpoint. He wrote as follows in 1948:

> History is read by different people for different reasons; it has many uses and values. To me its chief, but not its only value, is poetic. Its poetic value depends upon its being true record of the past. For the mystery of times past continually enthrals me. Here, long before us, dwelt folk as real as we are today, now utterly vanished as we ourselves shall vanish. History can miraculously restore them to our vision and understanding, can tell us a little of what were their hopes and fears, their words and works. . . . Forward we cannot see at all, backwards we can see fitfully and in part. In that strange relation between past and present poetry is always present, even in the most prosaic details. . . .

Trevelyan here emphasizes rather his own feeling as to the poetic or philosophic value of history. This is an aspect of the history of medicine that we need not dismiss lightly nor neglect. But his other remarks are, coming from him as our consultant historian, enormously important. The words "forward we cannot see" touch the core of the matter. All new truth is not only unknown or undiscovered; it must be, in a cold psychological scientific sense, unimaginable. Once its possibility is envisaged it is no longer undiscovered, since the mechanism of scientifific investigation exists to bring it to light.

Next we note his sketching of the method by which the past, which we can see "fitfully and in part", is to be used in the exploration of the future. Finally we notice his insistence on the necessity for scientific truth in history; upon that its use as a scientific weapon, just as much as its poetic value, entirely depends.

Galen, you will recall, perpetuated gross error in his description of the mechanics of the circulation for nearly a century and a half. He taught that the blood was formed in the liver and thence ebbed and flowed through the *vena cava* and portal vein to the right side of the heart and to the body generally. At the same time air from the lungs similarly ebbed and flowed through the left side of the heart and the arteries. The presence of blood in the air-conducting arteries after death he regarded as an agonal phenomenon. The only variation accepted was Guido Guidi's suggestion that the septa of the heart were perforated by minute invisible pores, allowing admixture of blood and air.

Harvey, we know, in 1628 discovered the truth as we now see it. There were of course predecessors: Ibn-an-Nafis, an Arab physician of the thirteenth century, Servetus in 1553, and perhaps most significant Cesalpino, all had glimpses of the facts. Cesalpino was the predecessor at Padua of the great Fabricius, under whom Harvey studied. But these were all forerunners. It was not till something, perhaps aided by hints from Cesalpino and the others, suddenly settled into proportion in the mind of William Harvey that the error of Galen was exposed. Harvey's scientific pursuit and demonstration of the truth that so came to him are in themselves not the least magnificent part of his work.

We, however, who have the mystery taught us as a commonplace, cannot help but wonder how such a strange and fantastic error lived so long. It is usually considered to be due to the enormous authority of Galen, which was

such that to question him was to court the fate of the heretic, the fate that befell Servetus. This, however, seems merely to beg the question. There were certainly other factors. One was this matter of man's mental blindness to completely new fact of which Trevelyan spoke. One was that the scientific approach was yet in its infancy as a tool; learning was then largely empirical and stemmed from the authority of great men. Another was almost certainly the fact that the information in that stage of the technical development of medicine and surgery was immaterial and irrelevant for practical purposes.

I would like now to speak of another historian and to show another aspect of the function of scientific history. You are all familiar with the story of William Tell. Mr. Samuel Baring-Gould, an historian, or as he prefers to call himself, an antiquary of the last century, has something to say on the subject. Here is the story in his own words.

> In the year 1307, Gessler, Vogt of the Emperor Albert of Hapsburg, set a hat upon a pole, as a symbol of imperial power, and ordered everyone who passed by to do obeisance towards it. A mountaineer of the name of Tell boldly traversed the space before it without saluting the abhorred symbol. By Gessler's command he was at once seized and brought before him. As Tell was known to be an expert archer, he was ordered, by way of punishment, to shoot an apple off the head of his own son. Finding remonstrance in vain, he submitted. The apple was placed on the child's head, Tell bent his bow, the arrow sped, and apple and arrow fell together to the ground. But the Vogt noticed that Tell, before shooting, had stuck another arrow into his belt, and enquired the reason.
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> "It was for you", replied the sturdy archer. "Had I shot my child, know that it would not have failed to reach your heart."

In the market place of Altorf in Switzerland there is, or there was in Baring-Gould's day, pointed out the site of the lime tree to which Tell's son was bound and a statue on the site where Tell stood to shoot. The story is one handed down to us over the centuries as an example of human courage and family devotion.

The only thing wrong with the tale is that it is untrue. There was, it is true, a man whose name we anglicize as William Tell who led an insurrection about that time. The episode of the apple, however, Baring-Gould concludes with almost a sigh of regret, is an old Aryan folk-tale which appears in the literature of many countries, centuries before Tell. Saxo Grammaticus, a Dane of the twelfth century, tells the same story of a warrior called Toki, the tyrant here being his own king Harald Bluetooth. It is told of Egil, brother of the mythical hero Velundr in the saga of Thidrick, and in many other Norse sagas. It occurs in King James of Scotland's "*Malleus Maleficorum*". It is told of that Harald who perished in 1066, with two or three different characters playing the role of Tell. It occurs in Finnish legend, with the variation that the brave archer is a precocious lad of twelve who saves the life of his aged father from bandits by a similar piece of accurate shooting. An English version is given in the ballad of William of Cloudsley.

There are other such tales. There is, or was, Baring-Gould states, a monument erected on Mount Snowdon to the memory of Llewellyn's dog Gellert, who, you remember, was slain by his master on circumstantial evidence after saving the life of his infant son from a fierce wolf. This particular tale is told in the "*Gesta Romanorum*", and by early Greek and Hebrew authors, originating, as far as can be ascertained, in the Sanskrit.

In this connexion I do not have to remind you that the story of George Washington and the cherry tree is not only an invention, but the flagrant invention of a minister of religion.

The great peril in this type of pseudo-history is the mingling of truth and invention. Tell, Llewellyn and George Washington were real enough, the incidents were pure fabrication, designed by some Pooh-Bah to add pseudo-poetry if not verisimilitude to his narrative.

It is the business of the scientific historian not only to discover and establish the truths of history, but in the process to demolish falsehoods, however beautiful. He must learn to winnow the grain of fact from the chaff of human invention. This is also the business of the scientific physician, and at times it is discouragingly difficult. There have been and still are William Tells and Gellerts in our medical skills and traditions, with monuments erected to them, which it is our constant duty to discredit.

Let me remind you of some of these which we have seen in the immediate past. At one time text-books of medicine in speaking of *tabes dorsalis* informed us that those fibres in the posterior nerve roots conveying proprioceptive impulses were especially vulnerable to the disease process. This idea sprang from a faulty correlation of two facts. The first was the wasting of the dorsal columns of Goll and Burdach in the disease, and the second the predominance of ataxia in the late symptomatology. *Tabes dorsalis* and locomotor ataxia were the pathological and clinical descriptive names of the disease. What was missed was that the spino-thalamic and spino-cerebellar tracts were protected from gross degeneration by the fact that there was a synapse in the cord between them and the posterior root ganglion cells. The clinical counterpart of this was the observation that the earliest signs in tabes are loss of light touch and pain sense over the butterfly area of the nose and cheeks and over the lower ulnar and fibular aspect of the extremities.

In cardiology we have seen many false doctrines perish: the idea that red meat exacerbated hypertension; the idea that complete bed rest was good and desirable in coronary occlusion and in cardiac failure; that quinidine was a dangerous drug in long-standing auricular fibrillation because it induced embolism from clots released in the auricle.

Other more worthy and thoughtful theories have fallen. The ingenious speculations of Sir Thomas Lewis as to the nature of auricular flutter and fibrillation were an attempt to correlate the facts relating to the rate and rhythm of ventricular contraction in these conditions, and the pharmacological action of digitalis and quinidine. We see now that the theory was bad, first because it multiplied hypothesis, against the doctrine of William of Occam, and more particularly because it implied that the simpler mechanisms now envisaged were, for some unstated reason, not physiologically possible. It was bad also since, even if a theory cannot be a working hypothesis leading to new discoveries of fact, it should be a convenient framework for generalization of the facts. I, and I am sure many students, have found it easier to remember the facts than Lewis's theory.

In the same way, but to my mind much more dangerously, Bramwell's theory of gallop rhythm tended to falsify rather than to clarify clinical fact.

Gallop rhythm, you will remember, was held to have a very bad prognostic import, since it was said to indicate a lengthening of the auriculo-ventricular interval with a shortening of the diastolic time of the heart to a point when the auricular sound coincided with the third heart sound. It could occur only at high pulse rates, and it could not occur in auricular fibrillation, by definition.

Now we know that a triple rhythm clinically indistinguishable from gallop rhythm can occur in all sorts of innocent and malign cardiac states. It can occur with a slow pulse in the bradycardia of the healthy athlete or in heart block. It can occur with rapid heart rates in mitral stenosis of minor degree, or when the left ventricle is labouring from any cause. It can occur in auricular fibrillation. The danger of Bramwell's theory was that this triple rhythm in any rapid regular heart, if called gallop rhythm, implied the presence of partial auriculo-ventricular block, and thereby gross myocardial damage, which in point of fact was not necessarily present. It is true that such a state of affairs as Bramwell described might exist, but it could be diagnosed only by electrocardiographic measurement of the intervals concerned, and thus, as a clinical tool, was worse than useless.

I speak perhaps with a little bitterness, since in my younger years to doubt the theories of Lewis and Bramwell was to court grave disapproval, and not to be able to remember them at examinations was a matter of peril.

Recently even more devastating heresy seems to be rearing its head. Glomset and Cross in Iowa became interested in bundle branch block and began to make sections of hearts to see what happened. They have come to the shocking conclusion that there does not exist in man a sino-atrial node, an atrio-ventricular node, or an atrio-ventricular bundle, Keith and Flack and Tawara and His notwithstanding.

Such a statement, of course, requires confirmation. If it is true, however, it will be a fearful condemnation of our scientific cardiological thinking, and at the same time will be an enormous relief to those who, like myself, can find no satisfaction in the various working hypotheses of electrocardiographic phenomena expounded from time to time.

Hypotheses are necessary in medicine. Only by such means can we generalize the vast mass of facts for the purposes of memorizing and of logical thought; and the hypothesis is, or should be, the working tool of the explorer in strange scientific country. The whole structure of medical science consists of a large body of fact, bridged over by a much larger body of hypothesis. Once we lose the sense of distinction between the two we are lost. No hypothesis should ever be asked to bear more weight than the facts upon which it is founded.

Let us turn now to a more pleasant and comforting aspect of the history of medical knowledge.

Some quarter of a century ago in Melbourne the use of X rays in the diagnosis of diseases of the heart was coming into its own. Some, of course, deprecated the innovation and foresaw the degradation of clinical wisdom by the use of such machinery. One of the points of interest which the remainder discussed was the curious stability in size of the healthy heart shadow. We knew that in an athlete the stroke volume of each ventricle might increase three times between basal conditions and violent exertion; that the difference in volume of the ventricles between the end of diastole and the end of systole could differ by as much as a third of a litre of contained blood. Why then did not this difference show radiologically? Nowadays, with the universality of cardiac screening, and even by a process of simple ratiocination, we can work out the answer, but it was then rather a mystery.

I have, however, never seen a clear and explicit account of the mechanism in any text-book or elsewhere except once, and that is in a course of three lectures on the heart delivered in Melbourne in 1864 by Professor George Britton Halford, the first professor of anatomy, physiology and pathology in the newly opened school of medicine in the University of Melbourne.

Halford was greatly interested in cardiology among many other matters, and he brought to it a scientific clarity which cannot be over-estimated. It began partly by his sharing an experience with William Harvey. Harvey once demonstrated to Charles I, who seems to have been most interested in medical matters, a young man with a sternal fissure, in whom the beating heart could be seen and felt under the skin.

In 1852 Halford, then a student, joined with three senior colleagues in presenting to the Royal Society the case of a certain Monsieur Groux, "a gentleman", states Halford, "in whom there existed a large sternal fissure, the skin alone covering the heart and the origin of the great vessels". From observations here and in animals Halford was able to describe the mechanics of the heart's motion as follows:

> During the systole or contraction of the ventricles the base of the heart approaches the apex. . . The ventricles contracting, the auricles simultaneously receive blood (from the great veins) and then occupy that part of the space within the pericardium previously taken up by the ventricles in their relaxed distended state . . . (while) the pericardial portions of the great vessels become suddenly elongated and distended.

Some five years ago I was privileged to watch Mr. John Hayward of Melbourne perform a left pneumonectomy on a young woman with tuberculous bronchostenosis. With the lung removed the left wall of the mediastinum was exposed, and it was obvious at a glance that there was no gross pulsation of the left ventricle in the usual meaning of the word. The contents of the pericardium remained practically constant in volume and shape, almost the only movement being that of a faint shadowed groove moving up and down the cardiac axis over about the middle third or so of its length. This groove was the moving edge of the valve-bearing fibrous plate, which in the heart acts as a piston, to its lower edge being attached the ventricular muscle, to the upper the auricles and the origin of the great arteries.

The heart, in short, as Halford taught nearly a century ago, remains at constant volume within the pericardium; as the ventricles empty the auricles and great arteries fill and *vice versa*. Increase in stroke volume is procured by increase in range of movement of the fibrous piston.

This mechanism is fascinating, and realization of its nature is indispensable to the understanding of many cardiological problems. The lowering of pressure in the jugular polygraph immediately after the *v* wave, which can be seen sometimes at the bedside as a systolic collapse of the veins of the neck, represents the sucking action of the strongly contracting ventricle in drawing blood into the auricle. The power of pericardial adhesions to cause cardiac hypertrophy becomes apparent.

Most interesting, however, is the light shed on the clinical sign of a systolic bruit in patent interauricular septum. We do not hear a diastolic hum as we might expect in this condition, but the swift systolic rush of blood from the left to the right auricle. The mechanism of the disability in patency of the interauricular septum depends upon a vicious circle established between the increased pressure in the pulmonary veins as compared with the systemic, and the resultant left-to-right flow through the opening. It has always been difficult to understand how the pressure difference is built up; it was suggested that the difference was due to the minute gravitational factor due to the normal superior position of the left auricle, but this seemed hardly adequate.

If, however, we visualize the forcible descent of the valve-bearing fibrous piston as accentuating even very small initial pressure differences, it becomes clear that an initial small difference of pressure and small interatrial flow can speedily build up by transfer of more and more blood to the pulmonary circuit into a large pressure difference and correspondingly larger shunt. From this it might be possible to suggest that surgical attack on the condition should lie, not in attempting to block the opening with tantalum or other methods, but to decrease pulmonary venous pressure by producing a minor degree of stenosis in the pulmonary artery. The degree of constriction produced would have to be delicately adjusted, as we know that any great degree of pulmonary arterial stenosis produces reversal of the flow in the interatrial septal defect and actual cyanotic heart disease.

It is pleasant to know that the problems arising in the radiology and mechanics of the heart so long ago really lay solved to our hand, had we had the wit to look for them. The pleasure lies in the fact that good scientific work remains for ever fresh and true.

Halford's lectures seem to me to represent the first major contribution to cardiology in Australia, and I feel that there are other lessons than the present one which he can teach us still. He was interested in the origin of sounds, especially the first sound, of the heart. Charles Williams had taught in 1835 that the first sound of the heart was of muscular origin, basing his views on experiments in which he pinned back the valves or opened the ventricle so that the valves were not forcibly closed during systole. Of these experiments Halford remarks that the theory "is based upon the most wretched experiments ever devised and supported by arguments of the homœopathic kind". His criticism was, we see, primarily historical—his refu-

tation lay in demonstrating that in the intact heart the first sound disappears when the great veins are occluded and the heart is allowed to beat empty.

Another aspect of the heart's work of which we have yet to realize the implication was his view of cardiac muscle relaxation, of which he wrote as follows:

> Relaxation of the muscular fibres of the ventricle is distinct from the relaxation of the heart's cavities; for how when the flow of the blood through the heart is stopped, and hence all force from without removed—how can the ventricular walls expand, how can the ventricular cavities be dilated? It is a physical impossibility and yet the globular form of contraction of the ventricles, and the lengthened form of relaxation, are distinctly seen, but no dilation can take place. Therefore in considering the order of occurrence in the heart's rhythm we must say that relaxation of the ventricles occurs previously to their dilation, and that these two conditions must not be confounded.

I wonder how many physiologists have noted this active lengthening of the ventricles during diastole in the empty beating heart, and I wonder how many cardiologists have paused to consider the import of this in ventricular dilatation and failure.

Halford did an enormous amount of work correlating the nature of the heart sounds in various creatures with the anatomical structure of the heart in question and its valves, visiting the London Zoo for this purpose. His affection for his subjects makes pleasant reading. Of the eagle he says:

> The bird I so often examined was a very fine specimen of aquila audax, an Australian bird. With the keeper he was quiet, and he soon began to know me, so that by the keeper taking him in his arms and holding his head slightly on one side, I have had my head at his chest for twenty minutes at a time.

Of the ostrich he remarks: "After many interviews I became tolerably intimate with four young ostriches."

Ths mechanism of the heart's action, so clearly described by Halford, does not seem, as I have said, to be ever explicitly described nowadays in books on the subject, nor do I find that students have any idea of it. Moreover, I have a sad suspicion that general medical ideas on the subject, if they exist, follow an older author. The classical description is "First of all the auricle contracts, and in the course of its contraction throws the blood . . . into the ventricle, which being filled, the heart raises itself straightaway, makes all its fibres tense, contracts the ventricles, and performs a beat, by which it immediately sends the blood supplied to it by the auricle into the arteries . . ." So wrote William Harvey in 1628. So think many of us today.

Why were Halford's teachings lost in the very school in which he taught? For the same reasons I imagine that Galen's error was perpetuated. Australian clinical cardiology (which in 1864 had not yet mastered the diagnosis of valvular disease or the use of digitalis) found them academic, unreal, irrelevant. The Harveian doctrine was sufficient for their simple needs. They did not look. They did not think.

What of us today? How many archaisms are we complacently harbouring; how many new truths are here before our eyes unseen? The answer of history is clear and insistent. They are innumerable.

Let us look at one or two of our problems, things we perhaps feel we understand a little. Quite apart from the plaque and hæmorrhage theory of coronary occlusion, how is it that cardiac infarction occurs without complete, or sometimes without even detectable, coronary artery blockage? Why are normotensive women spared? Why is coronary and not mesenteric or radial arterial occlusion the peril of the middle-aged male? Let us admit that we do not know and that also we cannot yet imagine why.

As another instance, take the nervous heart, or neurocirculatory asthenia, or effort syndrome, or Da Costa's syndrome. In that flowering of clinical wisdom in the eighteenth and early nineteenth centuries, Corvisart, that magnificent clinician, practised and taught the clinical methods of detecting cardiac enlargement and recognized that many people with apparent cardiac disease had normal sized and therefore normal hearts and that their disability was nervous and not cardiac. In England, Hope and Williams in the eighteen-thirties laid down the same doctrine. In 1871 Da Costa's memorable paper on the subject appeared, describing the nervous heart of soldiers.

During the Boer War there is as far as I can find no recognition or description of the condition in any of the accounts of the casualties in *The Lancet* or the *British Medical Journal*. During the 1914-1918 war the condition was again in the earlier years regarded as due to some organic toxin, to strain or to fatigue; only toward the end did the teaching of Hurst and others rectify the error. In 1940, after Dunkirk, I heard the subject discussed at a meeting of army physicians under the presidency of Sir Letheby Tidy, and again there were household names supporting the organic theory of the disturbance, just as later in the war they insisted on doing for the companion disorder of functional dyspepsia.

It was not, I think, till late in 1941 that Paul Jones set out the problem in his Goulstonian Lectures in terms that admitted of no doubt. The condition was due to psychological disturbance of the type of fear or anxiety, and was not due to disease of the heart.

Why has this major cause of disability been so regarded by the medical profession and by its victims? Is it because of the human shame of admitting the power of fear or anxiety to paralyse the usefulness of soldiers in the field? I would suggest that it goes deeper than this—that there is a deep psychological and philosophical background, which can be traced back into the farthest reaches of human history.

There is a division in the minds of men as regards their deeply held convictions on the problem of the relation of mind and body. On the one hand stand those who can accept a material, even a physiological, basis for mental and emotional events, and on the other those to whom such an idea is repugnant and horrible—who feel and know by deepest instinct that man is an immortal soul and his muddy vesture of decay, his body, merely the transient tool of the spirit. On this issue men have always formed into two camps, Platonists and Lucretians, materialists and idealists, tough-minded and tender-minded, mechanists and mystics.

According to whether you and I are of one or the other school, we will believe that anxiety neurosis and effort syndrome are unfortunate but comprehensible physiological breakdowns, or that they represent the failure of a poorly integrated soul to control his emotions and face his responsibilities.

I do not intend to discuss the pros and cons of the arguments. I would point out, however, that certain psychologists and psychiatrists have now demonstrated over and over again what can be done to the human soul, even to a soul of the attainments of a Cardinal Mindszenty. And I would suggest that there is an enormous onus, a great urgency, upon medicine and psychiatry to clear their practice and thought of legends and false doctrines and get to the facts. The only hopeful thing about the position is that if destruction is possible, then it carries with it the possibility that repair and reconstruction of the damaged mind and soul may also become so. At present I see no evidence that we are more than tinkering with the problem.

These two examples may perhaps illustrate in practical terms what a sense of history would teach us in general —namely, that our attainments, however great, are paltry enough compared with our ignorance. It teaches the scientific humility of which Newton wrote when he described himself as seeming to himself "like a boy playing on the sea-shore, and diverting myself in now and then finding a smoother pebble or prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me".

Again, a sense of history teaches us constantly to suspect error and to distinguish between fact and hypothesis mercilessly. When we are in doubt, history again directs us

to examine the evolution and life story of our facts and hypotheses for clues as to their true nature.

Further still, history gives us pertinent evidence of the manner in which mistakes have been made and perpetuated and victories won in that past into which we may look "fitfully and in part", in Trevelyan's phrase. It gives us thus a touchstone for the present and a method for the future.

Perhaps we may ask finally what were the factors that hindered development and discovery. First we must place the psychological barriers; the fact that the undiscovered is also the unimaginable; and that emotional factors, as in the case of neurosis, may corrupt the clarity of our vision and thought. Next we must place the factor of human authority like that of Galen in breeding complacency and forbidding reexamination of the facts as heretical. Next we must recognize that the tool of the scientific approach must be in well-trained hands to give results.

In practice what does history tell us positively that we must do? We must remember our ignorance. We must recognize as a fact that the undiscovered is by its nature unimaginable, and that all future gains will be made through facts now seemingly irrelevant. There are only three means of attaining to these unknowns—by the flash of genius of a Harvey, by the happy serendipity which can come only with unfettered research and thought, and finally by the tool of the scientific method.

Historical sense and historical erudition seem essential to the attainment of that scientific method and discipline in medicine by which alone we can repay our debt to the past and meet our obligations to the future. The successes and failures of the past can be, if we so will, a wholesome discipline in the present and a guide into the unknown.

References.

BARING-GOULD, S. (1884), "Curious Myths of the Middle Ages", Rivington's, London.

GLOMSET, D. J., and CROSS, K. R. (1952), "Morphologic Study of the Cardiac Conduction System", *Arch. Int. Med.*, 89 : 923.

HALFORD, G. B. (1864), *Aust. M.J.*, 9 : 225, 257, 289.

HORN, H., and FINKELSTEIN, L. E. (1940), "Arteriosclerosis of Coronary Arteries and Mechanism of Their Occlusion", *Am. Heart J.*, 19 : 655.

KING, E. S. J. (1952), "The Hæmodynamics of Subintimal Hæmorrhage", *Australasian Ann. Med.*, 1 : 18.

MACKERRAS, I. (1952), "Zoology and Medicine", *Aust. J. Sci.*, 15 : 16.

PATERSON, J. C. (1936), "Vascularization and Hemorrhage of Intima of Arteriosclerotic Coronary Arteries", *Arch. Path.*, 22 : 313.

TREVELYAN, G. M. (1949), "An Autobiography and Other Essays", Longmans, London.

WARTMAN, W. B. (1938), "Occlusion of Coronary Arteries by Hemorrhage into Their Walls", *Am. Heart J.*, 15 : 459.

WINTERNITZ, M. C., THOMAS, R. M., and LE COMPTE, P. M. (1938), "The Biology of Arteriosclerosis", Charles C. Thomas, Springfield, Illinois.

ON THE RECTAL ADMINISTRATION OF SODIUM THIOPENTONE TO CHILDREN.

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THERE can be little doubt in the minds of the medical staff connected with a pædiatric institution of the considerable psychological trauma of hospitalization of the younger child (Powers, 1948). That the effect of such trauma may last for a considerable period or even permanently after the child's discharge from hospital will be verified by the parents of many of these unfortunate children, and is the subject of a most illuminating paper by Wm. S. Langford (1948). The younger child up to the age of about eight years suffers most from the sudden deprivation of his maternal affection and protection, but children of all ages are liable to react violently to the unhappy stimulus of a painful or frightening diagnostic procedure or the suffocating terror of a forced ethyl chloride or ether induction. It is the sum total of his reactions to his admission to hospital and separation from his parents, the lack of sympathy and understanding of many members of the impersonal hospital staff, his penicillin injections and pathological examinations, and his anæsthetic that determines his over-all psychological response, while each separate procedure may leave imprinted on his conscious or subconscious mind a varying picture of fear.

The anæsthetist has a definite part to play in helping to prevent the fear response in the child receiving medical attention, for there is no doubt that anæsthesia has been in the past, and still is to a large extent, a most fearful procedure, and can be blamed in no small manner for subsequent maladjustment between the child and his medical advisers. Perhaps it is a pity that all practitioners have not in their tender years suffered the asphyxia, nausea and pungency of an inexpertly administered induction with its associated distressing vertigo and terrifying visual and auditory disturbances. A number of people describe their ether anæsthesias as being not particularly unpleasant. They are in the minority and were lucky to have been of placid temperament and to have had an expert administration. Repeated unpleasant anæsthesias are to be deplored in the child, who is often ignorant of what is to take place and, unceremoniously clamped on the operating table by several nurses, is plied with ether by an unknown bemasked doctor until such time as he has mercifully passed through all the stages of asphyxia. Under such circumstances the post-anæsthetic incidence in children of night terrors, enuresis and fear of the doctor is considerable. There are cases in which nightmares have simulated the visual experiences during induction of anæsthesia in a terrifying fashion. To be sure of the relationship of these responses to anæsthesia is difficult, except on a "post-hoc" hypothesis, but they occur sufficiently commonly to be suggestive. Claustrophobia may be a symptom extending permanently into adulthood.

There are several ways in which the thoughtful anæsthetist may help to prevent such an undesirable state of affairs. In general, the child from about five years of age and upwards is ready to listen to a simple explanation of what will happen to him when an anæsthetic is administered or when an unpleasant procedure is carried out. Provided he is prepared for discomfort, he will not be mistrustful of the medical staff subsequently, though he may dislike the procedure. Induction of anæsthesia should, if possible, be carried out away from the frightening environment of the noisy operating theatre, and in the older child can usually be performed with intravenously administered thiopentone.

It is, however, in regard to the younger child below about seven years of age that we are still left with the problem of overcoming the unpleasantness of the induction, though even in these children some expert anæsthetists can produce a quiet anæsthesia by not covering up the child's eyes while he is conscious, by the gradual approach of the mask to the face, and by the slow increase of anæsthetic concentration, all the while engaging the patient's attention with appropriate conversation. However, it is far better in the great majority of cases to employ some method of basal narcosis pre-anæsthetically, and it is because such basal narcosis has been used in my experience far too infrequently that this short paper has been written. At the Melbourne Children's Hospital I have been employing rectal administration of thiopentone successfully as an anæsthetic premedication for some considerable time. Certainly it is not a new procedure, and there are occasions when it is not the basal narcotic of choice, but the technique has been used so infrequently in this country that the attention of anæsthetists should be drawn to its wide application and value.

Not only is the procedure worth while in a psychological sense, but it yields dividends to the anæsthetist in terms of smoothness of anæsthesia induction and maintenance, while less of other anæsthetic drugs are used. This latter may be a spurious argument in some cases, but certainly is not so for patients with *diabetes mellitus* or with other conditions in which post-operative nausea and vomiting

should be kept to a minimum. The indications for its use are very definite in youngsters with epilepsy, who are known occasionally to be convulsed during induction. When regional or field blocks with cocaine derivatives are contemplated, it provides quiet working conditions and gives positive protection against the neurological effects of overdosage.

The Possible Objections to Any Form of Basal Narcosis.

As with practically any procedure in medicine, objections are raised to basal narcosis in general. They may be classified as follows.

When Rapid Recovery is Desirable.

Rapid recovery is desirable in operations round the mouth and pharynx, when there is the possibility of post-operative inhalation of blood.

Over a series of 26 cases of tonsillectomy performed at the Children's Hospital with thiopentone given rectally as a premedicant, it has been found that these children wake up almost as early as do those who have had no basal anæsthesia. Subsequently they return to sleep, but with an intact laryngeal reflex and at a time when bleeding has quite stopped. Of far more importance in the prevention of blood inhalation is careful operative technique with adequate suction, and the use of correct posturing and suction after operation by an intelligent and trained nursing staff.

Certainly, after very short procedures such as teeth extraction, post-operative recovery will be slow; but this procedure can often be carried out in children in a reasonably pleasant manner with nitrous oxide or with small doses of "Vinesthene".

Rapid recovery is desirable in chest procedures after which post-operative movement must be instituted as early as possible.

By the time most thoracotomies have been completed the effects of rectally administered drugs have usually vanished. After the shorter procedure of bronchography, persistent drowsiness is occasionally an undesirable feature of the post-operative period; again posture and suction are of greatest importance in the drainage of excess iodized oil from the bronchi. For these children, often subjected to repeated anæsthesias, basal narcosis is a justifiable procedure.

Rapid recovery is desirable in out-patient and casualty departments.

For very short procedures it is preferable to use nitrous oxide and oxygen anæsthesia to avoid delay in post-operative recovery. After longer operations carried out under ether anæsthesia, basal narcosis need add little time to the recovery period.

When Medullary Depression May be of Grave Significance.

After severe head injuries, when respiratory and circulatory depression is already present, any further depression of vital centres is to be avoided. Such patients are invariably comatose, and the question of basal narcosis prior to craniotomy *et cetera* should never arise.

Children with intracranial space-occupying lesions, and particularly those with a comparatively rapidly expanding lesion (for example, cerebral abscess), may be living on a knife-edge, so that any form of medullary depression may cause unexpected respiratory failure. When basal narcosis is thought necessary, paraldehyde is probably the safest drug to use, its respiratory depressant action being minimal.

In all types of shock, whether of traumatic, toxic or electrolytic nature, when circulatory depression is present with attendant stagnant cyanosis and perhaps incipient or developed pulmonary œdema, the administration of a depressant drug may not only worsen the circulatory failure, but by its respiratory depressing action may contribute further to the development of cyanosis and pulmonary œdema. Under these circumstances anæsthesia of any sort must be eschewed except in dire emergency.

Patients with respiratory obstruction, of whatever nature, should never have a basal narcotic administered. The result of unwise or excessive sedation is most dramatically illustrated in the child with glottic obstruction, who lives whilst able to use the accessory muscles of respiration, but dies when these muscles fail under the stress of exhaustion or in the relaxation of sleep.

Into this group, therefore, fall a number of patients in whom there are positive contraindications to the use of basal sedation.

When There May be Cumulative Effects with Other Sedative Drugs.

Occasionally one hears of a combination of narcotic drugs being used pre-anæsthetically (for example, morphine or an orally administered barbiturate combined with a rectally administered basal narcotic). For children, the depressant effect of such a combination may be severe, and the practice must be avoided.

When There is Reluctance on the Part of the Anæsthetist.

Reluctance on the part of the anæsthetist to use a technique which requires accurate timing and dosage is probably the commonest cause of the refusal to use basal narcosis—the anæsthetist simply cannot be bothered. The attitude is well exemplified by the student who asked why one bothered to use basal narcosis for children. To the reply that it made the induction less unpleasant for the child he said: "But surely the child has no say in the matter?"

The Rectal Use of Thiopentone in Particular.

For the last eighteen months thiopentone has been administered rectally as a basal narcotic to children between the ages of two years and seven or eight years in sufficient numbers for an opinion to be formed in regard to its efficiency, usefulness and safety. It has the following advantages over other basal narcotics in current use, which determine its greater range of usefulness: (i) It is more easily made up than bromethol ("Avertin"), the preparation of which requires considerable care and time. (ii) It is non-irritant at the concentration used, and does not degenerate into toxic end products as may bromethol. (iii) A very small total volume of solution is used, which only occasionally promotes an undesirable bowel action. (iv) It rapidly produces sleep, usually in about five minutes, and its time of administration can therefore be accurately determined. (v) There is no undesirable odour, nor does there develop the irritation of a high concentration of paraldehyde, which may occur when a closed circuit technique is being used. (vi) The incidence of undesirable side effects and of toxic reactions is low, and comparable with those of intravenously administered thiopentone used as an inducing agent. Delirium has not been encountered, though this is a not uncommon effect in children given orally administered barbiturates such as pentobarbital ("Nembutal") and "Seconal". Severe respiratory depression is rarely a feature, and hypotension is unusual (Weinstein, 1939). (vii) Recovery is comparatively rapid, owing presumably to quick redistribution of the drug from the brain to the fatty tissues, and perhaps to rapid destruction.

Rectally administered thiopentone is most useful in the age group two to seven years. Below the age of two years it is psychologically unnecessary, and moreover the dangers of airway obstruction in the young infant who is not being meticulously observed increase rapidly with the decreasing size of the trachea and larynx. From the age of about five years intravenous administration becomes more and more a reasonable technical procedure, and by the age of about seven years most children can be persuaded to have a needle (particularly as their otherwise hypodermic injection of atropine can be combined with the intravenous injection of thiopentone). This is preferable to rectal administration, as the dose can be more accurately judged.

The dosage employed has been twenty milligrammes of sodium thiopentone per pound of body weight given in a 10% solution in water, with a maximum upper limit of two grammes. For the older child (over about eight years) this dosage should be lowered slightly.

The technique of administration is simple in the extreme, but must be carried out with due regard for certain stringent rules. The first ruling is that the drug will not be administered unless and until all preparations for the management of an anæsthetic emergency are complete. This, of course, should be a routine procedure before the administration of any anæsthetic. Secondly, the drug having been administered, the child will be continuously under the care of a responsible person until anæsthesia is begun. Thirdly, no thiopentone must be given rectally unless the preparation of the drug has been carried out or supervised by the anæsthetist and the dosage determined and checked by him.

These rulings are commonsense precautions against emergency, are not irritating or laborious to the nursing or anæsthetic staff, and should not prevent the administration of thiopentone when the drug is indicated.

No preliminary enema is used, as this is usually unnecessary and adds a further burden to the small patient. Moreover, Weinstein (1939) suggests that thiopentone may be inactivated by soap suds. However, the child should be encouraged to empty his bowels prior to going to the operating theatre. The pre-operative hypodermic injection of atropine is given forty-five minutes before anæsthesia is induced; but all forms of sedation should be avoided when the rectal administration of thiopentone is contemplated.

The drug should be administered in the anæsthetic annexe of the operating theatre to avoid the possibility of any untoward occurrence during transit from the ward to the theatre. After preliminary chatter with the child he is turned onto his side on the trolley and the correct dose, drawn up in a syringe, is injected into the rectum directly through a well-lubricated number 10F catheter passed about two inches through the anus. The injection may be carried out quite rapidly, and is followed by a further injection of two millilitres of air to ensure complete emptying of the catheter, which is then withdrawn, and the room is darkened. The buttocks are not strapped together, though the precaution is taken of reapplying a square because of the occasional rejection of thiopentone. Even should this occur, it is usually not till the child is almost asleep, and failure to produce narcosis is rare. In general, unconsciousness supervenes within five minutes, and if the patient is not asleep within fifteen minutes experience has shown that he will not go to sleep later and anæsthesia is thereupon induced. It is important to realize that the child is only lightly sleeping, and induction must be carried out with care to avoid disturbing him. If he has been lying curled up on his side, anæsthesia must be induced in that position, as the disturbance of turning him on his back will be likely to waken him. For the same reason the surgeon must avoid examination of the child before anæsthesia is induced. Due care being taken, a smooth induction will result no matter what the anæsthetic agent employed, and after a smooth induction one can predict a delightfully quiet and even level of maintenance—the bumps seemingly being levelled out by the basal effect of the thiopentone, which lasts for about forty-five to sixty minutes. Respiration is quiet and rarely depressed with ether, though with cyclopropane there is early depression, which is a function of the cyclopropane as well as the thiopentone.

The only cases of severe respiratory depression seen in this series have been in older children, who have had a dose of 20 milligrammes per pound of body weight, and this for a child over the age of eight years is an excessive dose (*vide supra*).

Associated with the smoothness of induction there is a negligible incidence of laryngeal stridor or spasm, mucus secretion or cyanosis, which may often be features in poorly administered "open ether" anæsthesia. One must be aware of the continuing action of the thiopentone, which will be at a maximum about thirty minutes after its administration, and over this period the amount of anæsthetic drugs such as ether or cyclopropane necessary for adequate anæsthesia is necessarily reduced, sometimes to a very low level. One must be on one's guard to avoid excessive depth of anæsthesia.

Recovery after a very short procedure is prolonged, but in any procedure of thirty minutes or longer the rate of recovery of consciousness is not greatly affected, though the child may subsequently return to sleep for a considerable period, so making the recovery smoother and less nauseous than when basal sedation has not been used (Burnap, Gain and Watts, 1948).

Precautions, Complications and Contraindications.

The precautions to be observed before and during induction of anæsthesia have already been described. In particular the ordering of morphine or barbiturate derivatives beforehand should be avoided, as these in conjunction with thiopentone administered rectally may produce a dangerously deep level of anæsthesia.

The complications which we have seen or which have been described are few. Lorber (1950) describes one patient who aspirated portion of his stomach contents into his trachea, and another with severe coughing spasms and cyanosis. In this hospital there has been one case of laryngeal spasm following cocainization of the vocal cords, another following unsuccessful intubation, and a further one during induction of anæsthesia with ethyl chloride. Another child, in a similar way to a case described by Lorber, had coughing spasms and transient cyanosis during ethyl chloride induction, while two have exhibited respiratory depression of such degree as to prolong induction and produce cyanosis. Except for these last three, the complications are those which might be expected in similar circumstances when no basal narcosis had been used. In two further cases there was an excessively prolonged post-operative recovery period of twenty-four hours; but in each of these, in which operation had been performed for the repair of hypospadias, thiopentone was used intravenously as an adjuvant agent to "Trilene", and the total dosage of thiopentone was excessive. Theoretical complications of respiratory obstruction or failure before induction, or of a pronounced fall of blood pressure with circulatory depression, have not been observed or reported.

The contraindications to the rectal use of thiopentone are those of basal narcosis in general: the presence of local lesions in or about the rectum or anus, which preclude or render undesirable the giving of a rectal injection; injuries to the lower limbs or pelvis, in which movement of the patient is to be avoided; and the prior use of other sedative drugs. Though the catabolism of thiopentone is still *sub judicĕ*, it would seem undesirable to use the drug in the presence of gross renal or hepatic failure. Bronchoscopy is a relative contraindication, in that bromethol is more desirable, seeming to produce less reaction in the presence of severe bronchial stimulation.

Other Rectal Uses of Thiopentone.

Lorber has described his experiences in the rectal use of thiopentone for minor procedures and has found the technique very useful for the examination of fundi, for encephalography, for cystoscopy and for laryngoscopy.

Quantitative Evaluation of the Rectal Use of Thiopentone.

The accurate determination of the value of one anæsthetic technique as compared with another is notoriously difficult. In an effort to present the effectiveness of rectally administered thiopentone quantitatively, two series of cases have been assessed and are summarized below. The first series of 198 cases indicates its overall effectiveness and the complications of the procedure, and is partially compared with a series of 48 cases in which oral premedication with pentobarbital ("Nembutal") was used. The second series of 99 cases of tonsillectomy represents children who have been anæsthetized with and without pre-anæsthetic rectal sedation, and demonstrates the contrasting results of the two methods of anæsthesia.

First Series.

This series represents a group of 198 children between the ages of ten months and twelve years, of whom 52% fell in the most satisfactory age group, three to five years, 75% were in the group two to six years, and 88% were in the group one year to seven years. Six patients only are ten years of age or older. They are a consecutive group of children, all of whom have received thiopentone rectally in the dosage previously indicated prior to anæsthesia for a wide variety of surgical procedures of both major and minor degree, and whose conditions include a number of operative emergencies.

TABLE I.

Site of Operative Procedures (First Series).	Number of Cases.
Intracranial	9
Mouth, nose and throat	56
Thyroid	1
Other head and neck	11
Thoracotomy	2
Bronchoscopy and bronchography	28
Chest wall	4
Upper part of abdomen	9
Lower part of abdomen	9
Inguinal	14
Perineal	28
Extremities	27

Anæsthesia was subsequently continued with a wide range of drugs, the most common being ethyl chloride/ether, cyclopropane, nitrous oxide, "Trilene", with or without the addition of muscular relaxants, analgesics *et cetera*. Spinal analgesia was proceeded with satisfactorily in two cases.

Of the 198 children, 171 (86%) were asleep prior to the induction of anæsthesia, though 12 of them (6%) awoke sleepily during induction, 16 (8%) were drowsy prior to induction, while 11 (6%) failed to show any signs of sleepiness, or awoke so explosively during induction that the procedure was regarded as a failure. The partial or complete failure to produce sleep could be accounted for in six cases by the fact that the thiopentone or part thereof was rejected by the patient. However, the rejection of portion of the drug was not a constant cause of failure, as a number of children who subsequently slept satisfactorily were guilty of producing a fæcal return.

These figures compare favourably with those found in considering a small group of 48 children given oral premedication with pentobarbital ("Nembutal") in a dosage of 0·5 grain per stone of body weight (Table II). To increase the dosage of pentobarbital incurs a very definite risk of severe circulatory and respiratory depression.

TABLE II.

Condition.	Thiopentone.	Pentobarbital.
Children asleep or drowsy on induction of anæsthesia	186 (94%)	35 (73%)
Children asleep on induction of anæsthesia	171 (86%)	22 (46%)
Children remaining asleep on induction of anæsthesia	158 (80%)	21 (44%)

No complications arose prior to induction of anæsthesia in the 198 cases in which pre-anæsthetic thiopentone sedation was used.

Complications occurring during anæsthesia appeared in 23 cases. In 14 the complications could not conceivably be related to the thiopentone, as they consisted of such things as profuse hæmorrhage, coughing spasms during bronchoscopy related to excessive intrabronchial manipulation in children with chronic pulmonary lesions, technical mishaps with the anæsthetic circuit, and mechanical difficulties with airway maintenance. In the remaining nine cases, laryngeal spasm developed in three—in one during the induction of anæsthesia with ethyl chloride and "open" ether, in one following cocainization of the vocal cords, and in one following attempted tracheal intubation. Such reactions are common in the absence of thiopentone, which cannot therefore be reasonably blamed. One boy, aged ten years, showed some cyanosis during and after tonsillectomy performed under nitrous oxide, oxygen and "Trilene" anæsthesia, though his breathing was adequate throughout. Post-operative moist sounds had disappeared the following day. It is probable that he inhaled some blood; the anæsthetic seems not culpable.

There remain five cases in which thiopentone may be implicated. One child, who had an excessively active cough reflex, became temporarily cyanosed during induction of anæsthesia with ethyl chloride. After removal of his adenoids, whilst he was still lightly anæsthetized with "Trilene", he developed sudden respiratory arrest, requiring urgent tracheal intubation. It is probable that the respiratory arrest was due to a reflex associated with an excessive "Trilene" vapour concentration, rather than to the thiopentone administered rectally. Two further patients reached excessively deep levels of anæsthesia with temporary apnœa and cyanosis during bronchography whilst being anæsthetized with nitrous oxide, oxygen and ether. It is possible that the thiopentone was a factor in producing such excessive depth, which was, however, primarily due to an error in judgement.

Finally there were two children (one aged eleven years) who had respiratory depression of sufficient degree to make induction of anæsthesia for tonsillectomy with ethyl chloride and "open" ether a very slow procedure, so that the cough reflex was maintained too long for comfortable operating conditions. For this, thiopentone must accept full responsibility.

Of 198 cases, therefore, anæsthetic complications related to the rectal administration of thiopentone occurred in only five, of which in only two was the thiopentone primarily responsible. There were no deaths.

Post-operative complications developed in 21 cases. In 11 of these the complications were unrelated to the anæsthetic, being due to technical failures in the operative technique, post-cystoscopic urinary infections *et cetera*. Two children had rapidly diminishing minor respiratory infections, and one girl developed a pneumothorax and pulmonary collapse following ligation of a patent *ductus arteriosus* under cyclopropane and curare anæsthesia. Three further children vomited to a greater extent than usual, one with acute dilatation of the stomach (which is a constant feature after all his anæsthetics), one with transient ileus following resection of a Meckel's diverticulum, and one from unknown cause after bronchoscopy and bronchography. A thyrotoxic girl, aged two years, had tachycardia and cyanosis after cystoscopic examination with ineffective pre-operative sedation, whilst an infant suffered severe shock after the dressing of a large chest burn, in which anæsthesia was complicated by difficulty in maintaining an airway. Finally there were two boys, aged four years, who had hypospadias repairs carried out with nitrous oxide, oxygen and "Trilene" supplemented by intermittent intravenous doses of thiopentone. It seems probable that the twenty-four hours' sleep which these two boys had after operation was directly related to an excessive combined rectal and intravenous dosage of thiopentone.

Post-anæsthetic complications directly related to the rectal use of thiopentone occurred therefore in two cases, whilst a number of other complications arose as the result of the administration of a general anæsthetic in which the rectal use of thiopentone played only a minor part.

Second Series.

Together with other observers, I had felt that a definite incidence of such psychological upsets as enuresis and night terrors followed unpleasant anæsthesia. To test this theory and to demonstrate the rather more certain features of the patients' dislike for anæsthesia and fear of repeated anæsthesia, a series of patients premedicated with rectally administered thiopentone has been compared with another series anæsthetized without prior sedation. The patients

selected have been subjected to tonsillectomy and curettage of adenoids, prior to which they have all been admitted to the same surgical ward. Their nursing care has been supervised by one sister with a constantly changing nursing staff, the over-all hospital routine being identical for both series. By dealing with short-term patients treated (apart from the anæsthetic) in an identical way, I have avoided as far as possible variations in psychological reactions related to the nature of the nursing attention, and to prolonged or repeated stay in hospital.

The patients selected at random have been anæsthetized within the last eighteen months and have been reviewed at periods ranging from eighteen months to two months after their anæsthesia. Their parents were sent a circular letter and invited to attend a follow-up clinic. Those who failed to attend were subsequently sent a *questionnaire*, though this had the disadvantage that the children concerned were not personally questioned, and the replies obtained depended entirely on the parents, who were witnesses of varying intelligence. Of 26 patients given premedication with thiopentone, 21 attended the clinic, four returned *questionnaires*, and one failed to respond. Of 86 patients not so premedicated, 48 attended the clinic, 26 returned *questionnaires*, and 12 failed to respond. Whether the great difference in the response rate is due to variations in the children's reactions to anæsthesia is undetermined.

Group A, consisting of 25 patients given rectal premedication with thiopentone, were subsequently anæsthetized by ethyl chloride induction, "open" ether to surgical levels of anæsthesia and then maintenance by endopharyngeally administered nitrous oxide, oxygen, and ether or "Trilene". They varied in age from three to eleven years (though only four were aged over eight years), with an average age of 5·9 years.

Group B, consisting of 74 patients not given pre-operative sedation, were anæsthetized by different anæsthetists—resident medical officers and registrars of this hospital—with ethyl chloride induction followed by "open" ether to surgical levels of anæsthesia, and were then maintained with endopharyngeally administered nitrous oxide, oxygen and ether or air and ether. They varied in age from two to eight years, with an average age of 5·9 years.

During the interview, and also from the *questionnaire*, an effort was made to determine whether any psychological change followed anæsthesia, whether the child developed bed-wetting, restlessness or terrors at night, and whether he became frightened of doctors or of attending hospital and, if so, why. A careful inquiry was made as to whether the child remembered his anæsthetic and, if so, whether it was pleasant, unpleasant or left no particular impression. Finally it was determined whether the child was fearful of further anæsthesia. Some children said definitely that they were afraid of a further administration, whilst others, though they said they were not afraid, reacted most violently to the presentation of a mask soaked with ethyl chloride. These last were considered, by their reaction, to fear anæsthesia despite their previous statement to the contrary. The assessment of psychological changes had to be made, with full knowledge of the fact that in this particular age group there is, in the general child population, a gradual reduction in the incidence of enuresis and sleep disturbances, whilst changes in the psyche are frequently related to experiences at school and to maladjustments in the home environment. Furthermore, a large number of children were said to have been much more lively, easier to live with, happier *et cetera*, in direct relationship to a general improvement in physical health. Alterations in the psychological characteristics of the child were ascribed to the operative procedure only when they occurred in a clear-cut fashion after return from hospital.

Table III gives a clear indication of the child's personal feeling in the matter of anæsthesia. Unpleasantness of induction usually consisted of a "nasty" or "awful smell", and only occasionally were vertigo, aural or ocular phenomena, or suffocation mentioned. An occasional child, usually with a stable family background, considered his anæsthesia an enjoyable experience, whilst a few had no feeling in the matter. The difference between the groups in the numbers of children who remembered their anæsthesia is obvious, as is the difference between their fear reactions. The ratio is of the order of 3:1 in favour of the children who had been given premedication with thiopentone administered rectally. When prior sedation had been unsatisfactory and the child was awake at the time of induction the subsequent reaction was of the same order in the two groups.

TABLE III.
Reaction to Anæsthesia.

Attitude Towards Anæsthesia.	Group A: Premedication with Thiopentone (25 Cases).	Group B: No Premedication with Thiopentone (74 Cases).
Patients who remember anæsthesia:		
Anæsthesia unpleasant ..	5	43
Anæsthesia pleasant	1 } 7	6 } 63
Indifferent to anæsthesia ..	1	14
Patients who expressed fear of repeated anæsthesia (personal interview only)	3[1]	22[2]

[1] Out of 21.
[2] Out of 46.

An attempt has been made to summarize the changes for the better or worse in certain psychological features exhibited by some of the children following tonsillectomy (namely, enuresis, nocturnal restlessness, nightmares, and general mental state or psyche). In both groups there were a number of children who showed an improvement in both the diurnal and nocturnal psyche, which was related almost entirely to a corresponding improvement in general health consequent upon tonsillectomy and the increasing age of the child. On the other hand, Table IV illustrates the numbers of children who showed a psychological deterioration.

All three children whose enuresis grew worse after tonsillectomy were in group A. The first, a boy, aged four years, had an elder brother prone to soil his trousers, and the patient also had developed this complex as well as his enuresis. He also wept easily, and it seems that his psychological breakdown was related directly to the example of his older brother. The two other children simply showed exacerbations of a previously chronic enuresis.

Of four children who exhibited increased post-operative nocturnal restlessness (one in group A, three in group B), one had post-operative weight loss and worsening of a chronic nasal infection, two were particularly restless after seeing exciting films, and one was sleeping in unfavourable living conditions. It is unlikely that any of these children's restlessness was due to his anæsthesia.

Two children of group B had nightmares after operation; one was the boy mentioned above as living in unfavourable conditions. The second was a girl, aged six years, who for two weeks after returning home had night terrors in which she appeared to relive her anæsthesia.

There were eight children whose general psychological state deteriorated post-operatively (one in group A, seven in group B). The first was the boy who developed the soiling habit (*vide supra*). Of the seven from group B, two were simply stated in the *questionnaire* reply to be easily upset, and nothing further is known about these children. A boy, aged four years, had become hyperactive and had frequent dreams consisting largely of fantasies based on cinema experiences. A girl, aged eight years, had become less confident and more emotional, but her father was apparently of a very unstable temperament. Two girls, aged four and seven years, developed shyness though they were previously far from shy, and whereas the elder, who is a somnambulist, recovered from this after one month, the younger one is still a shy child. Finally, there was the girl, aged six years, mentioned previously, who relived her anæsthesia for two weeks post-operatively in

recurring nightmares, who is now a fearful and shy child, and cannot stand the smell of perfumes, cleaning fluids *et cetera*. Her mother is a nervous, deaf woman, who, however, tries her hardest for the child's sake.

An attempt to relate the development of claustrophobia to the suffocation of anæsthetic induction was abandoned, as it proved too difficult to convey the question to the child.

Fear of hospital attendance or of seeing a doctor was of approximately equal incidence in the two groups and seemed to be due almost entirely to the fear of needles, of being left behind as an in-patient, and of repeated out-patient attendances, particularly for aural infections. Only three children specifically mentioned their fear of anæsthesia, these children all having been anæsthetized without pre-anæsthetic sedation.

TABLE IV.
Comparison of Psychological Deterioration.

Disturbance.	Group A: Premedication with Thiopentone (25 Cases).	Group B: No Premedication with Thiopentone (74 Cases).
Enuresis	3	0
Restlessness at night	1	3
Nightmares	0	2
Diurnal psychological deterioration	1	7
Fear of hospital, doctors *et cetera*	7	24

It is difficult to come to any conclusion from the foregoing findings as to whether there is a reduced incidence of psychological trauma when thiopentone is given rectally before anæsthesia. The series is too small to be of certain value. However, it would appear, particularly in the case of the child who is incipiently psychologically unstable, or when there have been previous environmental stresses, that a distressing anæsthetic can initiate both short-term and long-term psychological reactions. This is particularly well demonstrated by the shy, fearful girl who had post-anæsthetic night terrors.

SUMMARY.

The child in hospital, deprived of his family protection, subjected to a variety of frightening procedures, and cared for by an impersonal medical and nursing staff, is apt to develop psychological changes. The anæsthetist has a part to play in preventing this, particularly by providing as pleasant an induction as possible. In the case of the younger child this is best carried out by means of some form of basal narcosis.

Objections are raised to basal narcosis, but except in a limited number of cases the advantages clearly outweigh the disadvantages.

Soluble thiopentone administered rectally to children in the age group two to seven years is of very considerable value and has advantages over other drugs used as basal narcotics. The technique is simple in the extreme, but the drug must be used with due care by the anæsthetist. Maintenance of anæsthesia is somewhat modified, as is the recovery period.

A quantitative estimate of the value of rectally administered thiopentone has been attempted by a consideration of two series of cases. The first series gives an over-all picture of the results and complications from the use of this drug in a series of 198 general surgical cases. It is an effective hypnotic agent and complications from its use are few. The second series compares a group of unpremedicated children with a comparable group premedicated with thiopentone, and it is shown that the fear of further anæsthesia is three times greater in the former than in the latter group. That there was a greater incidence of untoward post-anæsthetic psychological reactions in the former group is unproven, but the experiences of several children point to this probability.

ACKNOWLEDGEMENTS.

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REFERENCES.

Burnap, R. W., Gain, E. A., and Watts, E. H. (1948), "Basal Anæsthesia in Children using Sodium Pentothal by Rectum", *Anesthesiology*, Volume IX, page 524.

Langford, W. S. (1948), "Physical Illness and Convalescence. Their Meaning to the Child", *The Journal of Pediatrics*, Volume XXXIII, page 242.

Lorber, J. (1950), "Rectal Thiopentone in Children", *British Medical Journal*, Volume II, page 21.

Powers, G. (1948), "Humanising Hospital Experiences", *American Journal of Diseases of Children*, Volume LXXVI, page 365.

Weinstein, M. L. (1939), "Rectal Pentothal Sodium—A New Pre- and Basal Anesthetic Drug in the Practice of Surgery", *Current Researches in Anesthesia and Analgesia*, Volume XVIII, page 221.

ISONICOTINIC ACID HYDRAZIDE IN THE TREATMENT OF PULMONARY TUBERCULOSIS.

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IN January and April, 1952, the anti-tuberculosis activity in man of isonicotinic acid hydrazide[4] was reported by several groups.[1][2][3][4][5] The drug was first used in the United States of America in June, 1951, by Robitzek and his associates at Sea View Hospital, Staten Island, New York. It became available in limited quantities to us at Baltimore City Hospitals in February, 1952. By April, 1952, supplies were assured and a pilot study was undertaken in 20 cases of pulmonary tuberculosis.

Chemistry and Pharmacology.

Isoniazid is a chemically pure, synthetically produced substance with the general formula $C_6H_7N_3O$. It is an almost colourless crystalline compound highly soluble in water.

Its pharmacological status[5][6] is still largely undetermined. However, Benson[5] and his associates have shown that long-term administration of low concentrations of the drug in the diet of rats has no deleterious effects upon growth, gross appearance of the tissues, erythrocyte counts or hæmoglobin values. In dogs, long-term administration of isoniazid in higher concentrations did have some depressing effects on the reticulo-endothelial tissues and caused a significant drop in hæmoglobin values.

Rubin[6] and his associates have shown that isoniazid is completely and rapidly absorbed from the gastro-intestinal tract of dogs and mice. Within an hour after oral administration, the drug appears to be well distributed throughout the blood serum, cerebro-spinal fluid and pleural fluid. It is largely excreted in the urine. It disappears from the plasma completely in sixteen hours. No cumulation of plasma concentration was observed in a twice-daily schedule at four times the recommended and effective dosage.

On the basis of available studies, it appears that isoniazid is of low toxicity in experimental animals in dosage ranges which are at the same time effective. However, autopsy has shown that sixteen weeks' therapy at four to six times the recommended dose in dogs produced fatty degeneration

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[4] Officially designated isoniazid and so called throughout this paper. Supplied by E. R. Squibb and Sons and by Schering Corporation.

of the liver, less pronounced fatty degeneration of the convoluted tubules and a decrease in the erythroid cells of the bone marrow.

Dosage and Toxicity in Man.

At present the indicated daily dosage is from three to five milligrammes per kilogram of body weight divided into two doses, given orally. In these dosages isoniazid is rapidly absorbed from the gastro-intestinal tract, reaching its highest plasma concentrations in one and a half to three hours. From 50% to 70% can be recovered in the urine, excretion via this route reaching a peak in two to six hours. Appreciable and effective concentrations of the drug are present in the cerebro-spinal fluid within three hours of an oral dose in patients with or without meningitis. The recommended daily dosage gives rise to plasma concentrations of the drug which are considerably higher than those therapeutically effective in mice, as reported by Bernstein and his associates.[7] Moreover, if the analogy in experimental animals is carried another step, it would appear that the effective plasma levels and the toxic plasma levels are safely separated. As estimated by Burke, the ratio of the lethal dose to the minimal effective dose in experimental animals is 300:1 in the presence of satisfactory renal function.

In the dosage range recommended, mild toxic symptoms have been reported.[1][4][11] These may be grouped as follows: (i) Those due to sympathetic stimulation: muscle twitchings and tremors in the extremities, constipation, delay in starting the urinary stream, numbness and coldness of the extremities and exacerbations of preexisting peripheral vascular insufficiency. (ii) Those due to cerebral and psychic changes: vertigo, headaches, visual symptoms, changes in sleep habits, mental confusion and euphoria. (iii) Those due to hypersensitivity reactions: urticaria, skin rashes, intractable asthma and increased susceptibility to other drugs, especially of the atropine and epinephrine series.

To date, only mild signs of toxicity have been reported, in no case presenting a recognized pattern of drug toxicity. Slight drops in hæmoglobin concentration have occurred. Signs of mild renal toxicity (rises in blood non-protein nitrogen content, and the appearance of albumin, reducing substances and casts in the urine) have been reported. Liver function is unimpaired.

Antituberculosis Activity in Man.

A bulletin of the American Trudeau Society (March, 1952), distributed to members, listed the following changes to be expected in the clinical course of patients treated with the recommended dosage of isoniazid: reduction in fever, if present, in two or three weeks; reduction in cough; reduction in the volume of sputum and in the number of bacilli therein (as determined by examination of smears); gains in weight, appetite and strength; and some clearing of the reversible component of the pulmonary tuberculous disease by X-ray observation.

These changes were based on the experiences of clinicians at Sea View Hospital, New York, Cornell Medical Center, New York, and Indian Reservation Hospital, Arizona.

A more specific description of the results that one could expect with isoniazid, as described by Robitzek and his associates, is as follows: An average weight gain of 2·2 pounds per week per patient was recorded in a series of 44 studies over five to fourteen weeks. No patients lost weight. All 44 patients had elevations of temperature ranging from 100° to 103° F. and higher; 42 of the 44 had prompt return to normal in from two to twenty-one days, an average of ten days. All 44 had sputum prior to therapy, and 42 of them had sputum consistently containing tubercle bacilli on examination of concentrated smears. Twenty-three of the 44 lost all their sputum. Eight of the 42 with consistently positive sputum findings ceased to produce tubercle bacilli, even on culture of gastric contents. Twenty-two of the 44 had improved X-ray appearances, either diminished exudative disease (five cases) or demonstrable contraction of cavities (17 cases).

Development of Bacterial Resistance.

Since the first clinical reports were made, studies have been made on the emergence of tubercle bacilli resistant to isoniazid. Steenken *et alii*[9] reported resistant strains found as early as twenty-six days in chronic cavitary disease treated with isoniazid or its isopropyl derivative. Bacilli were grown on media containing 0·5 microgramme per millilitre, whereas growth was normally inhibited by as little as 0·125 microgramme per millilitre.

Combined Veterans Administration Army and Navy studies[10] on patients receiving isoniazid (150 milligrammes per day) reported resistant bacilli. They studied 108 patients for two to three months and 141 patients for three to four months. In the two to three months' study 46%, or 49, gave positive cultural findings; of these, 29% produced bacilli which grew on media containing 5·0 micrograms per millilitre. In the three to four months group 65%, or 91, yielded positive cultural findings, 51% producing resistant organisms.

Selection of Cases and Method of Study in the Present Series.

Twenty patients with active pulmonary tuberculosis were chosen; with one exception, their condition was stationary or progressive on or after other antibiotic therapy. The one exception was a previously untreated patient newly admitted. All the others had received streptomycin and para-aminosalicylic acid, and several had received viomycin. They were all considered clinically resistant to these drugs. There were nine white females, six Negro females, three white males and two Negro males. The ages ranged from fifteen to sixty-five years.

Prior to therapy, all patients were interviewed and an estimate was made of their clinical status. On the nature and extent of disease, fever, weight loss and symptoms, the condition of the 20 patients was classified as follows: "poor", eight patients—all had far advanced disease,[1] one with empyema and bronchopleural fistula; "fair", 10 patients—all had far-advanced disease, four having had surgical interference prior to therapy; "good", two patients —both with moderately advanced disease.

The daily dosage of isoniazid was either 150 or 200 milligrammes according to body weight, in two divided oral doses. Treatment was begun on groups of the 20 patients at weekly intervals from April 14 to May 11, 1952. All other drug therapy was suspended except in two cases as noted below. By October 6 the group had been followed for twenty-one to twenty-five weeks. At or immediately prior to that date the patients were again interviewed and examined, and a further estimate was made of their clinical status.

In association with isoniazid therapy, strict bed rest was given to all patients. One patient had a pneumothorax and two pneumoperitoneum, in all established prior to the study. One pneumoperitoneum was discontinued within two months because of complications.

The patients were weighed at the beginning of therapy and every two weeks thereafter. Intermediate nourishments were offered to all patients.

Ward nurses made a daily estimation of the amount of sputum produced, and records of the amount were kept on temperature charts.

All patients had base-line X-ray examinations, hæmograms, blood chemistry investigations and sputum cultures. The blood chemistry investigations in all cases included estimation of the non-protein nitrogen content, the total protein content, the albumin-globulin ratio, the thymol turbidity and cephalin flocculation, and many sodium, chloride and Van den Bergh determinations. The last three determinations were not followed up in all cases.

Results of Therapy.

Clinical Status.

Sixteen of the 20 patients noted a definite improvement in appetite and feeling of well-being. Generally, of the

[1] According to Diagnostic Standards, National Tuberculosis Association, 1950.

eight who started therapy in poor clinical condition, two remain in that category, while four moved up to the "fair" category and two moved up to the "good" category. One of these showed remarkable increase in appetite and feeling of well-being and lessening of fever, and gained 32·5 pounds in weight. Of the 10 patients in the "fair" category, two moved up to the "good" category. Both of the patients who started therapy in the "good" category improved somewhat.

Weight Gain.

If any weight gain of more than two pounds over the twenty-one to twenty-five weeks period is counted, 17 out of 20 patients gained weight. The largest weight gain for the entire period was 33·5 pounds at 1·3 pounds per week. Five patients gained 20 pounds or more in the period. The average weight gain for the entire period was 12·4 pounds. The average weight gain per patient per week was 0·5 pound. Two patients showed no weight gain, and one patient lost 0·5 pound.

Fever.

Prior to therapy three patients had no significant fever (that is, an occasional rise of temperature to 99° F.), five had rises of temperature to 99° to 99·5° F., two had rises of temperature to 99·5° to 100° F., and 10 had a rise of temperature of more than 100° F. After thirteen to fifteen weeks of therapy, all three without significant fever remained thus. Of the five with a temperature of 99° to 99·5° F., three showed no change and two showed temperature "spikes" lessened by 0·5° F. or more. Of the two with temperatures up to 100° F., neither showed any change. Of the 10 with a temperature higher than 100° F., nine showed temperature "spikes" lessened by 1° F. or more, and one showed no significant change.

In summary, of the 17 patients with significant fever prior to therapy, 11 showed significant change on isoniazid therapy. Further comment will be made below concerning the effects of therapy with additional drugs.

Sputum.

Eighteen out of 20 patients prior to therapy produced sputum in amounts varying from five cubic centimetres to two and a half cups per day. Two patients had never produced any sputum, and the amount raised by one patient has varied tremendously throughout therapy because of severe endobronchial disease. Of the 18 patients who produced sputum prior to therapy, seven showed no change in amount, four had sputum production eliminated entirely, and seven showed definite lessening of the amount. One patient had sputum production lessened from two cups full to 100 cubic centimetres per day.

Tubercle Bacilli in Sputum or Gastric Contents.

Twelve patients yielded consistently positive findings on culture of sputum or gastric contents prior to therapy, seven intermittently positive results and one consistently negative results. Of the first group, nine have continued to give consistently positive results, two have begun and continue to give consistently negative results on smear examination, culture and guinea-pig inoculation, and one has shown consistently negative findings with gastric contents, but has not had enough tests for the results to be significant. Of the second group, two have begun to give consistently positive results since therapy, two have continued to give intermittently positive results, two have begun to give consistently negative results, and one has yielded negative results with gastric contents but not yet enough to be of significance. The one patient who gave consistently negative results prior to therapy has continued to do so.

X-Ray Studies.

Of the 20 patients, 14 had exudative disease or cavities in which one could look for some change on serial X-ray films. The other six had either endobronchial disease or disease hidden by plumbage, thoracoplasty or pleural reaction. X-ray films were taken at intervals of four to six weeks. Those receiving pneumoperitoneum or pneumothorax were fluoroscopically examined at weekly intervals.

Of the 14 patients whose condition could be judged radiologically, seven showed some improvement. The previously untreated patient showed considerable absorption in her left upper lobe lesion. Two patients showed considerable reduction in cavity size, which was probably related to change in tension mechanism.

In the six patients who had obscuring factors, the following conditions were noted. One with thoracoplasty, one with obliterated pleural space, and one with lucite ball plumbage, all existing prior to therapy, showed no further detectable change radiologically. One patient with severe endobronchial disease and extensive atelectasis showed some slight clearing and improvement in aeration on the affected side, but worsening of her endobronchial disease according to bronchoscopic reports. Two patients underwent surgical treatment during the course of the study —one a Monaldi drainage and one lobectomy and modified thoracoplasty. Both showed considerable improvement, but the procedures precluded judgement as to the actual effect of isoniazid.

Urine Findings, Hæmogram and Blood Chemistry.

No significant urinary findings were discovered on frequent routine examination, including microscopic examination. Two patients were passing traces of reducing substance by the end of fourteen weeks' therapy. This condition disappeared in one case. Two began to pass albumin in trace amounts, but only transiently. One patient was a known diabetic, and his urine has, of course, contained reducing substance according to his diabetic status.

Hæmatocrit values rose significantly (five millimetres or more) in five cases, there was no significant change in 14 cases, and a moderate fall occurred in one case. The last-mentioned was a case complicated by empyema and bronchopleural fistula. In all cases except one the changes in hæmoglobin values followed along with the hæmatocrit reading, and in the one case mentioned the discrepancy was thought probably to be due to a laboratory error.

In all cases except three normal leucocyte counts were present in base-line studies. These three patients had varying degrees of leucocytosis (11,000 to 30,000 per cubic millimetre) throughout the study. Two were patients with complications (empyema and pelvic abscess), and one had far advanced disease, one lung being largely destroyed.

The non-protein nitrogen values showed no significant change in any case, all remaining within normal limits throughout therapy. The average total protein value was 7·0 grammes prior to therapy and 8·2 grammes after twenty-one to twenty-three weeks' therapy. This rise in most cases was due to a rise in serum albumin content. The values 7·0 and 8·2 grammes are compared with average values of 6·7 and 7·0 grammes obtained in our laboratory in two groups of 20 non-tuberculous patients, each picked at random, at the beginning and end of this study.

No patient showed significant change in cephalin flocculation or thymol turbidity determinations, though most of the patients showed some degree of alteration at the beginning of the study.

Toxicity.

Treatment was not suspended in any case. Two patients complained of occasional mild dizziness during therapy (before any additional medication was started), four developed slight drowsiness which they associated with the ingestion of the drug, and six patients developed muscle twitching in the extremities, but of mild degree. Two patients complained of slight constipation. One patient suffered a *grand mal* seizure during therapy, which to date is unexplained. The only other positive finding in this case is a slightly elevated cerebro-spinal fluid protein content. Further investigations are in progress. There were no headaches or skin manifestations attributable to the drug.

Additional Therapy.

Accumulating reports of emergence of bacilli resistant to isoniazid led us to believe that it was unwise to continue to offer all patients isoniazid alone. Therefore, as patients

came up for review after three or four months of therapy, we added streptomycin to the treatment of those who had not been proved streptomycin-resistant or had previous toxic reactions to it, and PAS or viomycin to others who could not receive streptomycin. Thus, nine patients received streptomycin, two patients received PAS, one patient received streptomycin and PAS, and three patients received viomycin, in addition to the isoniazid, the administration of these additional drugs being started at varying intervals after the initial three to four months' trial period. Two patients received streptomycin and PAS throughout the isoniazid therapy because of their initial clinical condition, and three patients have not been given additional therapy to date.

Many of the 17 patients who have now received additional drug therapy were started on these additional drugs too recently for any evaluation to be made. However, a few preliminary facts have been observed. The sputum output was lessened slightly in three of the patients who received streptomycin alone in addition to isoniazid, and no other change in sputum output has been seen in the other patient since the addition of the other drugs mentioned. Fever has been lessened further by the addition of streptomycin in the treatment of three patients who had shown an initial rise of temperature above 100° F. and who had shown a decrease of fever on isoniazid therapy alone. One patient who continued with a temperature above 100° F. in spite of isoniazid therapy has shown a fall of temperature to below 99° F. since the addition of streptomycin. No additional toxic manifestations have been noted. The effect on sputum conversion cannot be judged at this early date.

Two patients underwent chest surgery during the period of this study—one a Monaldi drainage and one a left upper lobe lobectomy and modified thoracoplasty.

Discussion.

The most significant result of twenty-one to twenty-five weeks' treatment of 20 patients with isoniazid has been their pronounced increase in appetite and feeling of well-being. This was almost uniformly commented upon by patients and noted by observers. Another pronounced effect was the reduction in cough and in sputum production. These results, while not so remarkable as would have been expected from previous reports, are encouraging. Chronically ill, wasting and even moribund patients felt, ate and slept better and coughed less.

While a 0·5 pound weight gain per patient per week is far below Robitzek's 2·2 pounds per week per patient, it is of significance in patients who have been going steadily down hill.

Reduction in fever was less remarkable than was expected. Of the 17 patients who had significant fever prior to therapy, the temperature of only one fell to normal and remained so, although 11 patients showed a significant decrease in the amount of fever.

The two items we were most interested in were changes in chest X-ray findings and reversal of sputum findings. We were discouraged with the poor response noted in the X-ray films. It is possible that there was less exudative component to be absorbed in some cases than there had been on previous streptomycin and PAS therapy.

Continued appearance of acid-fast bacilli in smears and cultures made isoniazid appear less effective than streptomycin. During the early months of streptomycin therapy we have found it most difficult to find tubercle bacilli by smear or culture.

Ease of administration, low cost and subjective and systemic improvement of patients under isoniazid therapy make it necessary to continue study with this drug. At the present time it has fallen far short of being the specific anti-tuberculosis drug.

Summary.

Isoniazid has been used at Baltimore City Hospitals for twenty-one to twenty-five weeks in 20 cases of pulmonary tuberculosis. All patients but one had received streptomycin and PAS for varying periods and were considered clinically resistant. Eighteen had far advanced and two moderately advanced pulmonary tuberculosis.

There have been pronounced subjective improvement in appetite and sense of well-being, a pronounced reduction in cough and sputum production, an increase in the serum protein content and some reduction in fever. The toxic effects of the drug have been minimal.

In 13 of the 20 cases, sputum findings have remained consistently or intermittently positive after twenty-one to twenty-five weeks' therapy. X-ray improvement was seen in seven cases.

Reports of emergence of bacilli resistant to isoniazid have caused us to add streptomycin, PAS or viomycin to the treatment in almost all cases.

References.

(1) Selikoff, I. J., Robitzek, E. H., and Ornstein, G. C. (1952), "Toxicity of Hydrazine Derivatives of Isonicotinic Acid in the Chemotherapy of Human Tuberculosis", *Quarterly Bulletin of Sea View Hospital*, Volume XIII, page 17.

(2) Robitzek, E. H., Selikoff, I. J., and Ornstein, G. C. (1952), "Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid", *Quarterly Bulletin of Sea View Hospital*, Volume XIII, page 27.

(3) Robitzek, E. H., and Selikoff, I. J. (1952), "Hydrazine Derivatives of Isonicotinic Acid (Rimifon, Marsilid) in the Treatment of Active Progressive Caseous-Pneumonic Tuberculosis. A Preliminary Report", *American Review of Tuberculosis*, Volume LXV, page 402.

(4) Elmendorf, D. F., Cawthon, W. D., Muschenheim, C., and McDermott, W. (1952), "The Absorption, Distribution, Excretion and Short Term Toxicity of Isonicotinic Acid Hydrazide (Nydrazid) in Man", *American Review of Tuberculosis*, Volume LXV, page 429.

(5) Benson, W. M., Stefko, P. L., and Roe, M. D. (1952), "Pharmacologic and Toxicological Observations on Hydrazine Derivatives of Isonicotinic Acid (Rimifon, Marsilid)", *American Review of Tuberculosis*, Volume LXV, page 376.

(6) Rubin, B., Hassert, G. L., Thomas, B. G. H., and Burke, J. C. (1952), "Pharmacology of Isonicotinic Acid Hydrazide (Nydrazid)", *American Review of Tuberculosis*, Volume LXV, page 392.

(7) Bernstein, J., Lott, W. A., Steinberg, B. A., and Yale, H. L. (1952), "Chemotherapy of Experimental Tuberculosis. V: Isonicotinic Acid Hydrazide (Nydrazid) and Related Compounds", *American Review of Tuberculosis*, Volume LXV, page 357.

(8) Selikoff, I. J., and Robitzek, E. H. (1952), "Tuberculosis Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid", *Diseases of the Chest*, Volume XXI, page 385.

(9) Steenken, W., junior, *et alii* (1952), "Mycobacteria Resistant to Hydrazines of Isonicotinic Acid", *American Review of Tuberculosis*, Volume LXV, page 754.

(10) "Chemotherapy of Tuberculosis", Quarterly Progress Report, Veterans Administration, Army, Navy Study with Appendix, July, 1952.

(11) Pembine Therapy Conference, Pembine, Wisconsin, September, 1952.

CONVALESCENT RUBELLA GAMMA GLOBULIN AS A POSSIBLE PROPHYLACTIC AGAINST RUBELLA.

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FOR several years convalescent rubella γ globulin has been available to medical practitioners in Victoria. The present paper discusses three clinical trials, and attempts to assess the value of the globulin when used under the conditions pertaining in clinical practice.

These conditions are that the globulin is given by the intramuscular route in a dose of four millilitres, and that it is given as soon as possible after exposure to the virus, but in any case within seventy-two hours thereof.

The first study has already been reported in part by McLorinan (1950). His figures appeared favourable, although in his report he emphasized that there were aspects of the work which made it impossible to place an exact interpretation on his results. The absence of a control series, a difficult matter to arrange in the circumstances, was felt to be an obvious weakness. Further, as stated in the previous paper, allowance had to be made for three factors before any final assessment of the full

protective value of the serum could be made: (*a*) Was the primary case really rubella? (*b*) Was the pregnant contact already immune from a previous unrecognized or forgotten attack? (*c*) Was the duration and intensity of the contact sufficient to have produced rubella if γ globulin had not been administered?

In the second study globulin was administered to a group of volunteers who had been artificially infected with rubella virus. Under these conditions the globulin appeared to afford no protection.

In the third study globulin was used in a controlled study of a natural epidemic of rubella. The results were consistent with partial protection, but the figures were not statistically significant. Korns (1952) has more recently examined three batches of γ globulin for a prophylactic effect in rubella. His globulin was made from pooled normal human serum. One of the three batches showed valid statistical evidence of partial protection.

Preparation and Use of Convalescent Rubella Gamma Globulin.

The γ globulin was prepared from human serum. Blood for this purpose was drawn from 264 adolescents and adults convalescent from an attack of rubella which began five to eight weeks previously. In each case the disease had been diagnosed by a physician, and most of the donors had acquired their disease during typical rubella epidemics in naval and military establishments near Melbourne. This blood was obtained by the Victorian Division of the Australian Red Cross Blood Transfusion Service, and sent to the Commonwealth Serum Laboratories, Melbourne, for processing.

Mr. F. J. Dempster, of the Commonwealth Serum Laboratories, prepared γ globulin as given in the following brief account. The plasma, separated by bucket centrifugation of the blood, was clotted by addition of calcium chloride to remove fibrinogen. To the resultant serum anhydrous sodium sulphate was added (180 grammes per litre). The precipitate containing the γ globulin was separated by filtration and dissolved in water, and the solution, after dialysis, was dried from the frozen state.

The concentrated solution of γ globulin (one-ninth the volume of the original serum) was then prepared by solution of the dried protein in normal saline containing 0·01% thiomersalate. Sterilization by Seitz filtration was followed by routine tests for sterility and toxicity.

The globulin was prepared in several batches from different sources. All these batches were used in the clinical trials reported both here and previously by McLorinan. One of these batches (batch 15) was also used in the experimental assessment recorded in this paper. This batch was drawn from 145 donors.

Clinical Assessment of Results of Administration of Gamma Globulin to Pregnant Women Exposed to Rubella.

Patients receiving γ globulin in pregnancy were all under the care of obstetricians or physicians in Melbourne. The request for γ globulin was made by the doctor in charge of the obstetrical patient, and in all the cases this request was granted without further inquiry. The history of contact and the diagnosis of rubella in the contact were dependent for their accuracy on the word of the pregnant woman in some cases, although whenever possible medical confirmation was obtained of the diagnosis of rubella. In presenting results of the clinical survey we include the figures presented in the previous paper by McLorinan, together with figures obtained since that time. Altogether 424 women said to have been exposed to rubella received two millilitres each of convalescent rubella γ globulin by intramuscular injection and were followed up. Five developed rubella. Similarly, of 388 who received four millilitres of γ globulin, four developed rubella. In summary, only nine women developed rubella of 812 who were said to have been exposed to the disease and who were given γ globulin.

In the nine cases in which protection was ineffective there was no obvious circumstance (for example, closeness of contact) which would have rendered the prophylactic procedure less effective than in other cases in which globulin was given with apparent success.

Attempted Protection in Experimentally Induced Rubella.

Volunteers for experimental infection were 23 female university students between the ages of eighteen and twenty-two years, and one aged twenty-six years. They all denied having had rubella previously, despite a carefully sought history of the disease.

The rubella virus which was used to induce the experimental infections was obtained from patients who were suffering from typical rubella. On the first day of the rash the patients gargled 10 millilitres of normal saline, which was then delivered into a container and mixed with two millilitres of beef heart infusion broth. The mixture was sealed in ampoules and frozen at −70° C. within ten minutes. It was stored at this temperature. Just before use it was thawed and mixed with penicillin to give a final concentration of 500 Oxford units per millilitre. It was administered to volunteers by atomized spray into the throat (0·1 millilitre) and in addition 0·1 millilitre was dropped into each nostril during inhalation.

The virus used in this work was a pool of two lots of garglings. The first lot was a mixture of garglings taken twelve months previously from two patients suffering from experimentally induced rubella. The second lot was obtained five months previously from patients suffering from experimentally induced rubella.

Procedure and Results.

Twenty-four volunteers with no history of rubella were infected on May 8, 1951, with rubella virus which had been stored for between five and twelve months at −70° C. Nine of the volunteers were then chosen at random and set aside as controls and designated group A. The remaining 15 volunteers were each given four millilitres of batch 15 γ globulin seventy hours after they had been infected (group B). The globulin was given by intramuscular injection into the lateral aspect of the thigh or the lateral aspect of the upper part of the arm. The weights of these 15 volunteers varied from 109 to 147 pounds, with an average of 128 pounds.

The two groups of volunteers were admitted to Fairfield Hospital on May 19, 1951, but at separate times of the day. This was eleven days after they had been infected. There was no contact between group A and group B on or after May 19. Both groups were observed daily until May 29, 1951, by one of the authors (S.G.A.), and both the authors examined all subjects suspected of having developed rubella.

Three cases of rubella developed in group A, the rashes appearing on days 13, 18 and 19 (average 16·2 days). Eight cases of rubella developed in group B with rashes commencing on days 15, 16, 16, 18, 18, 19, 19, 19 (average 17 days). The severity and duration of the rubella in group A were the same as in group B as far as these features could be assessed. No volunteer in either group developed rubella after leaving Fairfield Hospital on May 29.

Summary of Previous Experimental Infection.

By the use of the technique described in this paper several groups of "susceptible" volunteers have been infected with stored rubella virus by one of us in previous years (Anderson, 1949). The number developing overt rubella is shown in Table I.

Controlled Trial in a Natural Epidemic.

From May 12 to 17, 1952, 13 cases of rubella were diagnosed among a group of adolescent males living together in a Melbourne suburb. This appeared to offer an excellent opportunity to assess the efficacy of rubella convalescent γ globulin under controlled conditions in a natural out-

break. In the group there were 91 boys between the ages of fifteen and eighteen years who said that they had never had rubella. They had all been in more or less close contact with the recent cases of rubella which had occurred among their colleagues.

In order to obtain a reliable control group these 91 boys were divided at random into two groups. Group I consisted of 45 boys, group II of 46 boys.

Although the stocks of convalescent rubella γ globulin in Australia were nearly exhausted, Dr. F. G. Morgan, of the Commonwealth Serum Laboratories, and members of the Rubella Subcommittee generously agreed to the use in this outbreak of nearly all the remaining globulin. The batch used (batch 21) was made from a pool of serum

TABLE I.

Proportion of "Susceptible" Volunteers Developing Experimental Rubella in Previous Experiments.

Date of Experiment.	Length of Storage of Virus.	Number of Volunteers Given Virus.	Number of Volunteers Developing Rubella.
January, 1948[1] ..	1 month and less.	6	3
May, 1948[1]	3 months.	10	6
May, 1950	24 months.	5	2
December, 1950 ..	31 months.	10	7
Total	—	31	18

[1] Previously reported.

obtained from 50 volunteers between September 12, 1951, and February 11, 1952; although not all donors provided the same volume of serum.

The globulin was given to 45 boys in group I on the morning of May 16, four millilitres being injected into the left deltoid muscle. Concurrently the 46 boys in Group II received four millilitres of normal saline in the same fashion. Both the globulin and the saline were given by the same physicians, and the boys had no knowledge of which they received.

From May 19 to June 3 the 91 boys were inspected daily by one of the authors (S.G.A.), who at the time of inspection did not know who had received saline and who globulin. During this period of fifteen days 11 cases of rubella developed among the 91 boys (Figure I). Three of these cases were in boys who had received γ globulin on days 13, 13 and 14 after the injection, and eight in boys who had received saline on days 5, 9, 11, 12, 14, 16, 17 and 18 after the injection.

After June 3, boys who complained of any type of illness were examined by either the medical officer who attended twice weekly or by the nursing sister who was on duty every day. No case of rubella was recognized after June 3.

Discussion.

McLorinan has stated that clinical results with convalescent rubella γ globulin suggest that it is an effective prophylactic against rubella in early pregnancy. He has also discussed the factors which cast some uncertainty on his conclusions.

The degree of contact with the case of presumed "rubella" naturally varied considerably throughout the series of 812 women who received the γ globulin. The danger of rubella in pregnancy is widely known to the lay people in Victoria—probably more widely known here than in any other country in the world. We have no doubt that nearly all pregnant women who believed that they had come into contact with a case of rubella would have applied for, and been given, γ globulin while this material was available. They were all included in the series reported above.

It is not known what proportion of women of childbearing age in Victoria was susceptible to rubella in the period of this survey. Our experimental results over much the same period apply to girls aged between eighteen and twenty-five years, who, after careful consideration and questioning, still feel that they have not already had rubella. Of these, only about 60% are susceptible to experimental infection.

It is therefore held that McLorinan's early figures, which are included in the results of the uncontrolled trial in pregnant women published here, must be accepted with caution. While they suggest that γ globulin is effective in many cases, though not universally, this can be no more than a suggestion. Confirmation is required from a controlled trial.

With this position frankly in mind the Rubella Subcommittee of the Australian Red Cross Blood Transfusion

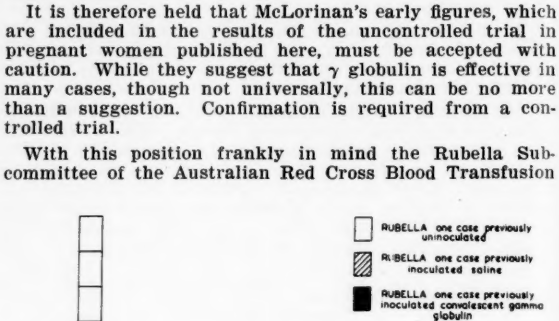

FIGURE I.

Service[1] requested a controlled trial of γ globulin (Morgan, Burnet, McLorinan and Bryce, 1950), and welcomed the inauguration of the experimental assessment reported in this paper.

The results of the experimental assessment of batch 15 must be considered against the background of previous experimental work with this disease (Table I). From this earlier work we can expect about 60% of presumed susceptible volunteers to develop the experimental disease under the conditions of our work. The percentage of clinical infections in the group B given γ globulin intramuscularly after infection is actually higher (eight "takes" among 15 infected) than the proportion of cases in the control group (three out of nine); but in neither case is the result significantly different from the 58% "take" in the previously published experimental work. If all experiments in Table I are considered together as forming controls for comparison with group B, or if group A alone is taken as the control group, there is no evidence of protection by γ globulin in group B.

Nevertheless the figures are too small to allow a definite conclusion that the globulin was of no prophylactic value. For example, if we consider these experimentally infected volunteers as forming a self-contained experiment, there is a 1 in 20 probability that either such an experimental result, or a more divergent result, will be obtained in the face of a real protection rate of 36% by the globulin. This figure rises to about 50% if the facts of Table I are allowed as a valid control.

However, the most probable conclusion is that under the conditions of the experiment the batch 15 of γ globulin did not appear to prevent or modify the incidence of clinical rubella.

Two factors must be considered, however. The first is that this trial attempted to assess the efficacy of only one batch of globulin, which had been stored at 4° C. for approximately twenty-one months between the taking of the blood and use. The second factor is the manner of experimental infection of the volunteers. The size of the infecting dose is not known, but it may have been large. It may have been considerably larger than would normally be acquired during accidental natural exposure to rubella.

[1] The members of this subcommittee are Dr. Lucy Bryce, Sir Macfarlane Burnet, Dr. H. McLorinan and Dr. F. G. Morgan.

If this was so, it might be argued that γ globulin given seventy hours later would be less effective in an artificial infection than it would be in clinical practice. Whereas on theoretical grounds this did not appear particularly likely, nevertheless it was clearly necessary to find some means of assessing the effectiveness of γ globulin against natural infection by the use of adequately matched control and treated series.

The study made in the boys' institution appeared to fill this need. If globulin is to be of value in the prophylaxis of rubella in pregnancy, it must be able to prevent rubella when administered between one and three days after infection has occurred. Therefore, in the interpretation of the present results the primary question to be decided is whether the injection on May 16 prevented the development of those infections which were initiated on May 13, 14 and 15. For this purpose we may assume an incubation period of between ten and nineteen days to the appearance of a rash (Anderson, 1949). The subjects with whom we are concerned would be expected to develop a rash between May 23 and June 3. During this interval there were seven rubella patients in the control group and three in the globulin group. The case occurring on May 21 is excluded as being too early.

A statistical examination of this result shows, firstly, that the difference between the globulin and the control groups is not significant ($P = 0{\cdot}17$), secondly, that the most probable protection rate based on this result is 57% of those given γ globulin, and, thirdly, that this result, or one more divergent, is consistent within the 1 in 20 probability with a maximum protection rate of approximately 90%.

Thus there are three lines of evidence regarding the efficacy of γ globulin given within seventy-two hours after exposure to rubella. Firstly, the uncontrolled clinical trial in pregnant women indicated that globulin might have protected nearly all exposed to rubella; but this interpretation was admitted to be subject to considerable doubt. Secondly, apparently no protection was afforded by γ globulin (batch 15) against experimental infection with rubella virus. Thirdly, although the most probable interpretation of a controlled trial in an epidemic was that one person in every two was protected against rubella, the figures for the control group and the globulin-treated group did not differ to a statistically significant degree.

A much larger series of figures in a strictly controlled trial would be necessary to define more closely the role of γ globulin in rubella prophylaxis. The available results are admittedly consistent with a prophylactic effect of globulin in a proportion of cases; nevertheless, it is almost equally likely that the globulin used did not prevent rubella in any instance.

Under the circumstances the continued preparation and use of convalescent γ globulin for the prophylaxis of German measles in pregnancy needs reconsideration. When a new preparation for the prophylaxis or treatment of disease is suggested for general use, it is usual to demand, firstly, that the active principle can be assayed chemically or biologically in the laboratory so as to ensure uniformity of different batches, and, secondly, that in controlled clinical trials a fully significant beneficial result can be demonstrated.

On these two criteria the use of γ globulin for the prophylaxis of rubella in pregnancy cannot yet be recommended. If, in the future, a means can be devised for titrating antibody to the virus, new information might warrant reopening the matter. On the other hand, the use of convalescent globulin over the past four years in Australia has been widespread and has undoubtedly brought mental comfort to many women. We cannot exclude the possibility that by its use a small number—probably at most about 1% of those injected—may be spared the distress of a congenitally damaged child.

On these grounds it may be considered wise to continue to prepare γ globulin from the serum of convalescent rubella patients, and to make such globulin available for use at the discretion of the medical practitioner concerned.

Summary.

In three trial series γ globulin has been made from convalescent rubella serum and used prophylactically against rubella.

In an uncontrolled clinical trial doses of two millilitres or four millilitres of globulin were given to 812 pregnant women after accidental natural exposure to suspected rubella. Only nine developed rubella from their contact. The majority of these cases have been previously reported by McLorinan.

However, the globulin appeared to be of no prophylactic value against artificially induced rubella in a group of 15 non-pregnant young women.

In a controlled trial in a natural epidemic globulin was given to 45 potential contacts, and 46 received a control injection. Eight controls and three "globulin" patients developed rubella. The results are discussed.

Acknowledgements.

We are very grateful to Dr. J. J. Graydon, of the Commonwealth Serum Laboratories, Melbourne, for helpful criticism and statistical analysis of the results. The members of the Rubella Subcommittee of the Australian Red Cross Blood Transfusion Service have given valuable advice during the preparation of this paper. We are grateful to the Australian Red Cross Blood Transfusion Service, and to Mr. F. J. Dempster, of the Commonwealth Serum Laboratories, Melbourne, for the γ globulin employed. We are indebted to Dr. A. Taylor and Dr. K. G. Chatfield for valuable assistance.

References.

Anderson, S. G. (1949), "Experimental Rubella in Human Volunteers", *The Journal of Immunology*, Volume LXII, page 29.

Korns, R. F. (1952), "Prophylaxis of German Measles with Human Serum Globulin", *The Journal of Infectious Diseases*, Volume XC, page 183.

McLorinan, H. (1950), "Diagnosis and Prognosis of Rubella", THE MEDICAL JOURNAL OF AUSTRALIA, Volume II, page 390.

Morgan, F. G., Burnet, F. M., McLorinan, H., and Bryce, L. M. (1950), "The Preparation, Distribution and Use of Anti-Rubella Gamma Globulin", THE MEDICAL JOURNAL OF AUSTRALIA, Volume II, page 490.

Reports of Cases.

SUDECK'S POST-TRAUMATIC OSTEODYSTROPHY OF LIMBS.

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> Disease as it stalks through the land cannot keep pace with the incurable vice of scribbling about it.
>
> —JOHN MAYOU, 1688.

THE post-traumatic osteodystrophy of Sudeck, though fortunately a rare complication, may follow any injury, trivial or severe, to the soft or bony tissues of the limb. After a varying latent period there may appear a characteristic symptom-complex in the affected extremity. This usually starts in the region of the hand or foot, but it may commence anywhere in the limbs—for instance, the knee, shoulder or elbow. The lesion commences with constant burning pain of a causalgic nature, which is present at rest and made worse by movement and is out of all proportion to the injury. Painful muscle spasm then ensues, affecting the muscles governing the distal joints of the limb so that these are unable to be moved. This spasm may be abolished by general anæsthesia or the exhibition of the relaxants. Later, periarticular adhesions

may supervene causing ankylosis of the affected joints. Swelling of the limb due to œdema of the subcutaneous tissues occurs. Pronounced osteoporosis of the limb skeleton is found, and in the later stages this may affect the joint surfaces, causing them to fuse. An accompanying vasomotor imbalance completes the picture. There is first vasodilatation of vessels, causing an increased blood flow to the extremity, with redness and an increased skin temperature. Later sympathetic over-action may occur and the limb is cold and pale, with excessive sweating.

Case I.

The patient was an apparently healthy man, a bread-carter, aged thirty-six years, married, and with one child. I first examined him in May, 1950, when he gave the following history. In February, 1950, the wheel of a bread-cart ran over the toes of his left foot. He produced radiographs taken at that time, which showed that he had sustained a comminuted fracture of the tip of the distal phalanx of the third toe with slight separation of the fragments, and a chip fracture of the lateral aspect of the base of the distal phalanx of the fourth toe in good position. The fractures were simple and he was treated by active weight-bearing movements without plaster, with apparent success.

In April, 1950, five weeks after the accident, he first noticed pain with stiffness, weakness and coldness of the left foot and toes. This pain was present at rest and was made worse by exercise. Swelling of the foot quickly followed, and he noticed that it sweated excessively. The foot was never warm, red or throbbing at the commencement of the illness, as has been described by many authors on this subject. Treatment was by physiotherapy, including massage and active weight-bearing movements; but it was of no avail. No other relevant facts were elicited in the history, the patient always having had good health. However, at the age of eighteen years he had sustained a fracture of the proximal phalanx of the right great toe when kicking a football. This fracture was unsuspected until radiographs were taken of the right foot and leg for purposes of comparison with the present injury. The fracture of the toe was then found to be ununited, sclerosis of the bone ends being present. This fracture had never caused him any trouble whatever.

Examination of the patient in May, three months after the accident, showed that, compared with the normal right foot, the left was swollen up to the ankle with firm, slightly pitting œdema. The skin was pale, but otherwise normal in appearance, being neither shiny, smooth nor atrophied. The pallor remained constant in any position of the limb. The affected foot was cold and moist with sweat, whereas the other was warm and dry. Pulsation could not be felt in either the anterior or posterior left tibial arteries, whereas it could be felt in the right. The foot was held stiffly in slight plantar flexion and eversion. there was both active and passive limitation of the ankle, tarsal and toe movements. What movements of these joints were present were very weak and painful. This lack of mobility was due to intense spasm of all muscles below the knee. Movements of the knee and hip joints were normal. He walked with the aid of crutches, as weight-bearing on that leg intensified the pain. The right leg was normal. There were no other relevant abnormal physical findings.

A full-blood count gave normal findings, and the blood failed to react to the Wassermann test.

Radiographs of both lower limbs showed a normal bone structure of the right lower limb, except for the ununited fracture of the great toe. The fracture of the left fourth toe was healed, but that of the third was ununited, sclerosis of the fractured ends being present. The left tarsus, tibia and fibula appeared normal, except that there was a small punctate translucent area in the superomedial angle of the talus.

The patient then disappeared for three months, to reappear in August, 1950, six months after the accident. Meanwhile, he had been treated in plaster without benefit. The clinical picture now was essentially the same as before, except that the œdema was massive, extending from the toes to just below the knee. A radiograph showed the fracture of the left third toe to be still ununited. There were now punctate osteoporotic changes present on the dorsal aspect of the first metatarsal bone, with pronounced irregular demineralization of the tarsus, tibia and fibula. The femur was unaffected. The small punctate area previously present in the talus was now seen to be part of the general osteoporosis.

In October, 1950, conservative treatment being unavailing, a left lumbar sympathectomy was performed with removal of the second and third ganglia by the extraperitoneal route through a muscle-splitting incision. The foot and ankle joints were also manipulated under the general anæsthetic. These joints were able to be put through a full range of movement, owing to relief of the muscle spasm.

The immediate post-operative course was most gratifying. The day after operation the foot and leg were red, warm and dry, and the pulsations of both tibial arteries were easily felt. The joints were able to be moved more freely, both actively and passively, through an almost full range of movement, owing to the lessening of pain and muscle spasm. During the next week the œdema greatly diminished. Active exercises were instituted, and he was able to walk unaided without pain, though with a limp, a week after operation.

Improvement continued until the day after he returned home in November, 1950, one month after his operation, when the pain, muscle spasm and œdema suddenly recurred as badly as before operation. The only difference now was that the foot and leg were still warm, red and dry, with palpable tibial arteries. The condition of the limb gradually but unrelentingly deteriorated and in July, 1951 (seventeen months after the accident), the character of the œdema changed, in that the skin below the knee, instead of being smooth, became thick and rough, with firm non-pitting œdema. The œdema had changed from a venous to a lymphatic type—a change which may have been due to the sympathectomy. The foot was still warm and dry (see Figure I). In October, 1951, radiographic examination showed severe generalized osteoporosis of disuse atrophy type involving all bones below the knee. In addition, it was noticed that the lower third of the femur was becoming atrophic. All joint surfaces were normal.

As the condition of the leg was becoming progressively worse, treatment with cortisone was instituted in consultation with Dr. I. A. Brodziak. Two hundred milligrammes were given the first day, followed by daily injections of 100 milligrammes until 1·5 grammes had been given. This dosage was followed by 50 milligrammes daily for one week, then another 50 milligrammes every second day until a total of four grammes had been given. The only effect this had was to make the œdema a little softer by November, 1951. However, one week later, the œdema, though softer, was more pronounced and had risen to just above the knee (Figure II). The pain and spasm were not relieved—in fact, they became worse. By this time the patient's morale was very low and he was almost bedridden from the pain and weight of the leg. Consequently, in December, 1951, it was decided to amputate the leg.

Ablation was performed through the thigh, a ten-inch length of femur being left with equal antero-posterior skin flaps. Care was taken to cut the flaps above the level of the œdema, because if this is not done the flaps fail to heal, so that reamputation is necessitated. The femur appeared to be unaffected on macroscopic examination through the plane of section.

Convalescence was complicated by some causalgia and "phantom leg" sensation, in spite of the previous sympathectomy. These symptoms decreased in intensity over the next eight months, but did not entirely cease. The flaps healed by first intention and never became œdematous. When the patient was last examined, in July, 1952, the stump was ready for an artificial limb.

On examination of the leg, the skin was thickened and nodular up to the knee. There was gross œdema of the subcutaneous tissues. The muscles appeared to be normal on macroscopic examination. The bones, when cut, showed

areas of patchy osteoporosis. The fracture of the third toe was found to be united by fibrous tissue. The joints were normal. The vessels, arteries and veins were dissected out and appeared normal. There were no clots in the lumina. The nerve trunks were normal. On microscopic examination a skin nodule showed the characteristics of neurodermatitis. There was cellular infiltration of the upper corium, mostly by lymphocytes and plasma cells. Swelling of the papillæ was present, so that the rete pegs were pushed apart and thickened. The capillaries were normal. Examination of the subcutaneous tissue showed œdema only. The muscles were normal, as were the vascular system and nerve trunks. Examination of sections of the bones revealed only patchy osteoporosis.

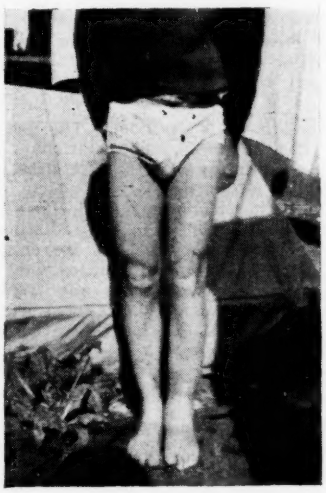

FIGURE I.

Case II.

In contrast to the previous patient, the following is the clinical history of a patient who sustained Sudeck's atrophy following a Colles's fracture of the right wrist.

This patient was a married woman, aged sixty-five years, who was first examined in January, 1948, when she had fallen over on her outstretched right hand, sustaining a classical Colles's fracture with avulsion of the ulnar styloid process. Radiographs showed that the bones of the wrist and forearm were otherwise normal. The fracture was reduced into satisfactory position by manipulation under general anæsthesia. The usual padded forearm plaster cast was applied with the wrist in slight dorsiflexion, and supervised active movements were commenced.

Four weeks later the fracture was firmly united clinically. However, movements of the fingers, which had been practised assiduously under almost daily supervision, had never become full. Radiographic examination showed that the fragments were in good position and that union was not yet complete. It showed also a pronounced stippled osteoporosis of the bones of the hand, fingers and forearm. Though no pain was present, and the fracture site was not tender, it was decided to continue with plaster immobilization and active exercises. Two weeks later still, the plaster cast was removed. The fracture was now united both clinically and radiologically. However, the patient was now complaining of constant pain on the anterior aspect of the hand and forearm. Finger movements had regressed and were now painful. The fingers were held in flexion, owing to spasm of all muscles below the elbow. The fingers, hand and forearm sweated more than usual and constantly throbbed. They were red and slightly swollen from œdema. The pulsations of the radial artery were readily palpable.

The diagnosis of Sudeck's osteodystrophy was made. In spite of intensive active exercises the condition worsened, but the patient refused any other treatment. Six months after the original injury the condition became stabilized, becoming neither better nor worse. It continued in this manner over the next three years until the patient became lost to view. During all this time the limb was always painful, with stiffness of the fingers and wrist. This rendered the limb clumsy, but it was still useful. There was no impaired sensation or paræsthesia. Sweating was not excessive and the limb gradually became normal in colour and was always warm. The swelling also gradually disappeared. Radiographs taken in October, 1951, showed that the fracture line was no longer visible. There was pronounced generalized osteoporosis (no longer stippled) of the bones of the limb below the elbow.

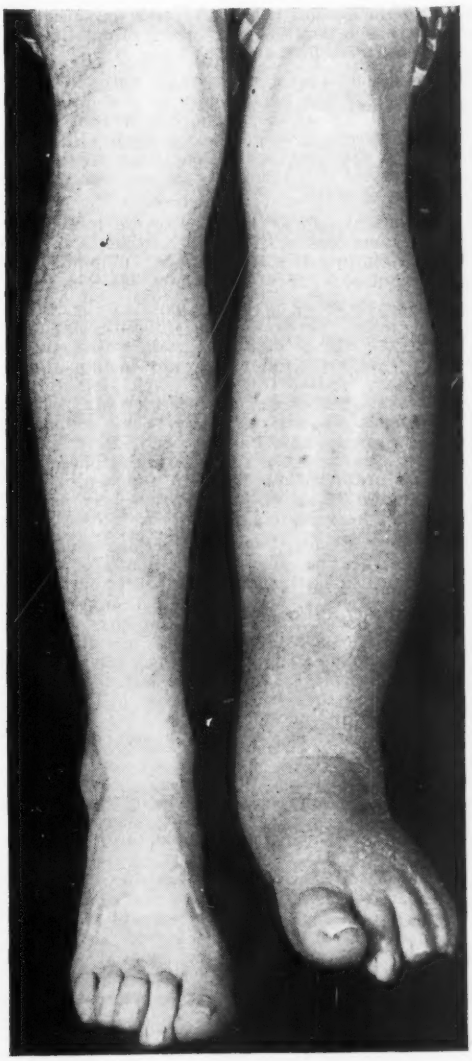

FIGURE II.

Comment.

Though both these cases may be diagnosed as of Sudeck's osteodystrophy, they differed considerably from each other. The second case was the milder, more common type of Sudeck's osteodystrophy of the upper extremity associated

with a fairly severe lesion—namely, a Colles's fracture. This patient was able to be observed for a period of nearly four years, during which time she refused all but the simplest treatment. After six months the condition reached a stationary level, becoming neither better nor worse, except that the signs of sympathetic atrophy gradually cleared up. However, the pain, stiffness and bone atrophy never decreased. Nevertheless the limb was useful, though clumsy, in contrast to that of the first patient. A further contrast was the comparative absence of œdema in the second patient, possibly because gravity does not play such a large part in the circulation of the upper limb as it does in that of the lower.

This patient sustained this lesion in spite of intensive active exercises of the upper limb, so that it could not be due to a neglected disuse atrophy, as Watson-Jones considered such cases might well be in 1943. However, in 1952 he agreed that Sudeck's lesion was a specific entity, and even suggested that it might be one of the diseases of the adaptation of Selye.

The first patient had a far more severe lesion, though the initial trauma was much less than that of the second patient. In spite of all treatment, amputation was eventually required.

There are a number of interesting points to be considered in the first case. There was the fracture of the right great toe at the age of eighteen years, which, though it did not unite, was never followed by any complications. On the other hand, similar fractures of the left third and fourth toes sustained at the age of thirty-six years were followed by Sudeck's osteodystrophy. This differed from the classical descriptions, in that the œdema was more marked than usual and there was no initial phase of vasodilatation. However, according to Stephenson (1951), either vasodilatation or vasoconstriction may accompany this disease in its early stages.

Conservative treatment by active exercises and again by immobilization had no effect on the course of the lesion in either case. In Case I, lumbar sympathectomy overcame sympathetic overactivity at least until amputation was performed, but had only a very temporary effect (one month) on the pain and muscle spasm; nor did it prevent causalgia and "phantom limb" sensations after amputation of the limb. Treatment by cortisone had no effect at all on the unrelenting course of the disease in Case I.

Discussion.

Ætiology.

Examination of the amputated limb of the first patient gave no information at all as to the cause of this lesion. It was originally thought to be inflammatory, but more recently attention has been focused on the sympathetic nervous system for a cause. The Leriche school believed that vasodilatation led to decalcification, and hence they ascribed the osteoporosis and other aspects of this disease to this cause. Also, since these lesions go on to vasoconstrictive effects (which in some, as in Case I, may be present *ab initio*), they postulated that the disease was due to overactivity of the sympathetic nervous system and treated it by periarterial sympathectomy. This was shown by Middleton and Bruce (1933) to have a very temporary effect only, and they advocated lumbar sympathectomy, not only for cure of the sympathetic side-effects, but also for the pain and muscle spasm as well. However, we can see from Case I that though the signs of sympathetic overaction were changed by the sympathectomy to those of paralysis, the pain and spasm were relieved temporarily only, and the œdema and osteoporosis not at all. From Case II we can also see that over the three years that the patient was able to be followed up, the signs of sympathetic dysfunction gradually righted themselves, whereas the pain and muscle spasm persisted.

Consequently, sympathetic malfunction is only a minor part of the clinical picture, its relief doing nothing to halt the onward march of the lesion, whose chief manifestations, therefore, the pain and the spasm, appear to be mediated rather by the somatic nervous system.

Radiographic Changes.

Although the name, osteodystrophy at joints, serves to focus attention unduly on the bone changes, these are merely those of an unusually severe and rapid disuse atrophy, which is all the more remarkable because of the usually trivial lesion initiating the sequence of events.

The abnormal radiographic appearances commence in the lower limb, as in Case I, in the talus, followed by the tarsals and metatarsals, and then in the tibia and fibula. In the upper limb they commence, as in Case II, in the wrist and fingers, to be followed by the radius, the ulna and the humerus. The changes appear first as discrete little spots of stippled-like osteoporosis, owing to the spongiosa being affected first.

The radiographic appearances in these cases were so typical it was not considered necessary to reproduce the radiographs here.

Treatment.

No specific treatment is available. The disease appears to progress (Case I) or become stationary (Case II), whether one uses splinting or active exercises. Sympathectomy helps only in mitigating the side effects of overaction of the sympathetic nervous system, as in Case I. Cortisone in Case I was without effect, in contradistinction to the two patients successfully treated by Dwyer (1952) with cortisone and ACTH. Case II illustrates what happens in a comparatively mild case without any treatment other than active exercises. Case I shows what happens in the severe case, in which all treatment save amputation was without avail.

Prognosis.

Even comparatively mild cases, like Case II, have a poor prognosis, because residual disability—namely, pain and stiffness—are always left (Klser-Sven, 1947). The more severe cases, especially those in the lower limb (like Case I) go on to amputation, and provided that this is carried out above the level of œdema, the flaps will heal well and the patient can be rehabilitated.

Summary.

Two cases of Sudeck's osteodystrophy, one of the leg and one of the arm, following trivial trauma, are reported. The case of Sudeck's osteodystrophy of the arm followed a Colles's fracture. After six months it settled into a chronic stationary phase, which did not alter in the three years during which it was observed. In the other case Sudeck's atrophy occurred in the leg after two trivial toe fractures, one of which failed to unite. It progressed to amputation in spite of lumbar sympathectomy and cortisone therapy.

Acknowledgements.

I wish to thank Dr. Colin Graham, morbid anatomist at the Royal North Shore Hospital, for performing the examination of the amputated leg in Case I. I wish to thank the photography department of the Unit of Clinical Investigation for the photographs.

References.

DWYER, A. (1952), "Sudeck's Atrophy and Cortisone", *M. J. Australia*, 2: 265.

KLSER-SVEN (1947-8), *Acta orthop. scandinav.*, 17: 253; quoted by Stephenson, *loco citato*.

MERCER, W. (1950), "Orthopædic Surgery", Fourth Edition, Edward Arnold and Company, London.

MIDDLETON, D., and BRUCE, J. (1933), "Post-traumatic Osteodystrophy at Joints", *Trans. Med.-Chir. Soc. Edinburgh*, New Series, 48: 49; quoted by Mercer, W., *loco citato*.

STEPHENSON, W. (1951), "Some Complications of Colles' Fracture and their Treatment", *Post Grad. M. J.*, 27: 627.

WATSON-JONES, Sir R. (1943), "Fractures and Joint Injuries", Third Edition, E. and S. Livingstone, 1: 62; (1952), Fourth Edition, 1: 54.

A CASE OF CONGENITAL DYSLEXIA.

By S. J. CANTOR, D.P.M.,
Melbourne.

THE following are notes of an unusual condition, the pathology of which has been reasonably well ascertained. The main features include defective vision, epilepsy and a psychotic reaction. The patient had been taught braille to a limited extent because of his visual defect. He has been diagnosed as suffering from object agnosia and visual verbal agnosia.

Clinical Record.

Early History.

The patient, a male, now aged seventeen years, has the following family history. The mother is stated to be hysteroid. The father died when the patient was aged nine years. An identical twin brother of the patient was found to have an intelligence quotient of 80, and he has always been in advance of the patient developmentally. An elder sister is married, and is stated to be apparently dull. A younger sister is normal.

At an institute for the blind the patient learned to weave and to take part in sports. Recognition of pictures was found to be inadequate. He could rarely identify anything in pictorial form. His colour vision was normal. His dark adaptation was abnormal, indicating probably defective peripheral vision. Depth perception and perspective perception in pictorial form were very defective. It was found that over the years his perception was improving. This was largely the result of learning to trace with his eyes. Electroencephalographic findings were as follows. The first report was that the electroencephalogram was non-epileptic in type. In view of Nielsen's assertion that visual verbal agnosia is invariably associated with a subcortical lesion below the major angular gyrus and separated from the calcarine area, a second electroencephalogram was taken. A grossly abnormal record with a dominant epileptic type of rhythm was noted. Photic response was entirely absent. No spike activity occurred.

In visual agnosia tests almost all objects were correctly named. Tactile agnosia tests, with objects protected by a shield so that the patient could feel but not see the object, were passed successfully. His performance in the object-sorting test was abnormal, and consistent with that expected from an organic psychotic. The overall defective level of performance was associated with evidence of ability for high-level abstract conceptualation.

From the foregoing and other tests it was considered that the patient was a moron and that he was an epileptic with a probable cortical or subcortical lesion in the area of the major angular gyrus. The absence of gross abnormalities in a consistently abnormal record in conjunction with the indications of a definite focus were suggestive of a subcortical lesion. The patient displayed visual verbal agnosia, but did not display object agnosia, at either visual or tactile level. He was unable to cope with the simplest organization of perspective; and he was unable to integrate a number of isolated percepts in pictorial form. He was, however, able to integrate percepts of real objects. His ability to recognize in general terms was apparently improving considerably with time.

Recent History.

The patient was admitted to the Mental Hospital, Sunbury, from the Receiving House, Royal Park, in April, 1950. Before certification he had attacked his mother and brother, as well as a neighbour. He had also threatened to take his own life. He had had major and minor epileptic fits since childhood; latterly he had had about one fit a week.

His physical condition was as follows. The heart action was regular. There was a rough systolic murmur at the pulmonary area. The lungs were normal. He was in ordinary good health. Neurological examination showed him to have active reflexes. The plantar reflexes were flexor in type. The pupils were equal in size and they reacted to light and to convergence. Vision was defective. The fundus was normal in each eye. There was a small refractive error only. The fields of vision were full. There was no ocular explanation of his defective vision. The response to the Wassermann test was negative.

Psychiatric examination revealed that the patient was cooperative. He said that he had wanted only to frighten his relatives and not to harm them. There were indications of a degree of mental defect. He was orientated. He was regarded as suffering from visual agnosia, with mental defect, epilepsy and social maladjustment. A psychological report indicated that he was passively cooperative. His intelligence quotient was 58; on another occasion it was set down as 70. His ability for comprehension and for abstract and verbal concept was high. His visual perception was much worse than he said. Tests showed that he was unable to describe or name most of the parts in picture cards. His immediate memory span was very defective. He was classified as a moron. Stereoscopic vision was found to be absent; no strabismus was present.

Progress.

He has remained in good health and has become suitably adapted in the environment of the mental hospital. Examination of the fundus of both eyes shows very distinct arteries. A fine reticular structure is seen in the retinæ. He makes constant slight frowning movements as well as movements of the head. Slight facial mannerisms are also present.

Discussion.

In view of the discrepancy between the findings of examiners over the last ten years and of the apparent near-blindness manifest before his admission to the institute for the blind, it has been thought that the possibility of hysterical amblyopia as a complicating factor must be considered. It has been suggested that the patient has epilepsy and visual verbal agnosia, and that his true visual disability has been made the tool of an hysterical personality in coping with or escaping from a difficult family environment. This additional complication of morosis may be considered as prolonging the appearance of object agnosia. Finally, Neilsen's assertion that visual verbal agnosia rarely occurs with any other agnosia, and then usually with unilateral tactile agnosia, and his claim that brain abnormality is always causative and that the site of the lesion varies with different agnosias, is quoted as being apparently relevant to the final diagnosis in this case.

Acknowledgements.

This case report has been compiled with the assistance of notes made by the staff of metropolitan hospitals, as well as mental hospitals, and also by the patient's teacher at the blind institute and by psychologists at the Psychology Department of the University of Melbourne. To these notes the writer is greatly indebted. Permission to publish these notes has been granted by the Mental Hygiene Authority, Victoria.

Addendum.

The patient was tested with a "Viewmaster" stereoscope with "Kodachrome" transparencies. In a view with tall trees he saw a man (who was not in the picture). He did not see stereoscopically. Then he began to see moving figures of light; he became irritable and walked away. Hallucinations of vision had therefore been produced by the stronger stimulus of the coloured transparencies. On a subsequent occasion when the same stereoscope was brought to him he was afraid to look through it (stereoscopophobia).

A CASE OF "ANTHISAN" POISONING.

By E. M. BROADFOOT,
Senior Resident Medical Officer, Royal Alexandra Hospital for Children, Sydney.

I WOULD like to record a case of "Anthisan" poisoning in a patient admitted to the Royal Alexandra Hospital for Children, Sydney, on March 31, 1952.

The patient was a previously healthy girl, aged two years. The following history was obtained from the parents.

The child was put to bed at 5.30 p.m. She was seen at 6 p.m. and appeared normal. However, when she was seen again at 7 p.m., green marks were noticed on her face and bed-clothes. It was then realized that she had been eating the "Anthisan" tablets which had been prescribed for the treatment of her father's hay fever. Eleven of the 0·1 gramme tablets were missing, and presumed to have been swallowed. At this stage she appeared normal and was given a salt emetic with no result.

About 8.15 p.m. it was first noticed that the child was not well—she looked "queer" and complained of tightness in her chest. Ten minutes later convulsions began. She was given 0·75 grain of phenobarbital by intramuscular injection and an ether anæsthetic, but the convulsions were not controlled. Her stomach was washed out, after which she was brought to the Royal Alexandra Hospital for Children at 11.15 p.m., cyanosed, unconscious and in convulsions. Death occurred fifteen minutes after her admission to hospital.

The case was reported to the City Coroner, and an autopsy revealed congestion of the brain and kidneys and œdema of the lungs with petechial hæmorrhages.

The following chemical findings were reported by the Government Analyst. The active content of each tablet was 1·1 grains of pyranisamine. The stomach and intestine contained 0·08 grain of pyranisamine, the spleen, kidneys and liver 0·06 grain, and the gastric washings 0·3 grain.

The onset of symptoms in about two hours with death in five hours is similar to other recorded cases of poisoning by antihistaminics. Usually the onset of convulsions has been from half an hour to two hours after ingestion, and has been preceded by signs of cerebral depression or irritation. Deaths have usually occurred from two to fifteen hours after ingestion of the drug. In fatal cases in children convulsions usually occur, whereas in adults they are uncommon, depressant effects being more obvious. Under the age of two years antihistamine drug poisoning has been usually fatal.

Unfortunately there is no known specific antidote, and apart from evacuation of the stomach contents treatment is symptomatic. It is suggested that sodium bicarbonate left in the stomach will delay absorption. As a result of a review of the literature and animal experiments, Wyngaarden and Seevers recommend "Pentothal" to control the convulsions followed by caffeine and ephedrine sulphate in the depressant phase; however, they add that ether may be preferable, since there is less respiratory depression than with the barbiturate.

This death is reported with the object of emphasizing the danger of allowing children to have access to antihistamine drugs.

Acknowledgement.

I would like to thank Dr. S. E. L. Stening for permission to publish this case and for his advice.

Reference.

WYNGAARDEN, J. B., and SEEVERS, M. H. (1951), "The Toxic Effects of Antihistaminic Drugs", *J.A.M.A.*, 94: 277.

Reviews.

Manual of Electrocardiography. By Benjamin F. Smith, M.D.; 1952. New York: Elsevier Press, Incorporated. 9″ × 6½″, pp. 228, with 119 illustrations. Price: 32s.

SINCE the war there has been a steady stream of books on electrocardiography from the United States, and Texas has now furnished another. "Manual of Electrocardiography", by Benjamin F. Smith, M.D., is, according to the preface, used in teaching students of the College of Medicine of Baylor University. The general plan of the book for the most part conforms to that of similar books, but differs in emphasis. One-quarter of the book is devoted to a correlation of electrocardiographic and autopsy findings, but it is disappointing to find that in this chapter there is no history or electrocardiographic diagnosis and that the text is given over to tiresome morbid anatomical reports which have not been edited. The chapter on acute *cor pulmonale*, borrowed entirely from Sodi-Pallares, is refreshingly short. The last chapter, "Pen Pictures of Cardiology", departs from the main subject and suffers from over-simplification; it is a little startling to read that "murmurs and thrills in infants and young children are of no diagnostic significance". It is also hard to follow the reasoning whereby a section on "Cyanosis and Clubbed Fingers of Congenital Heart Disease" should be devoted entirely to one case of acyanotic ventricular septal defect.

The electrocardiogram illustrating atrial septal defect is taken from a child two months old and is certainly not typical, nor is evidence given that the diagnosis was correct. Neither the original electrocardiograms nor the reproductions are consistently good, and the text is obscured at times by neglect of the conventions of English construction. Nevertheless, the book is sound in substance. Unfortunately the class notes from which the book grew have not been edited sufficiently, and for this reason it is unlikely that it will come into general use.

Fitness for the Average Man. By Adolphe Abrahams, O.B.E., M.D., F.R.C.P.; 1952. London: Christopher Johnson. 7½″ × 5½″, pp. 174. Price: 10s. 6d.

SIR ADOLPHE ABRAHAMS, well-known physician and honorary adviser to the British Olympic athletic teams, has published a volume entitled "Fitness for the Average Man". He devotes chapters to the meaning of "fitness", training, food and feeding, diet in athletic training, alcohol, tobacco smoking, injuries and disabilities of sports and games, health talks, "Too Old at Forty?", "Infant Prodigies of Sport", women in athletics, amateur or professional, the psychology of record breaking, "doping", and brain and brawn. The book is interestingly written and, while intended for general consumption, should be acceptable to medical readers. They may not agree with everything he says, but must acknowledge his very wide experience. The chapter entitled "Health Talks" contains a good deal of interesting material and should be helpful to those who have to prepare popular lectures.

Textbook of Gynecology. By Emil Novak, A.B., M.D., D.Sc. (Hon.), F.A.C.S., F.R.C.O.G. (Hon.), and Edmund R. Novak, A.B., M.D., F.A.C.S.; Fourth Edition; 1952. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9″ × 6½″, pp. 812, with 523 illustrations. Price: £4 16s. 9d.

THE fourth edition of this book is presented under the dual authorship of Emil Novak and his son Edmund. It is virtually a replica of the third edition in that it embraces the entire field of clinical gynæcology without reference to surgical technique. The manner of presentation is unaltered and there is the same richness of excellent illustrations. Indeed, the book is as worthy as the great name of its author. It is, however, difficult to justify the issue of a new edition. There is undoubtedly some additional information, particularly concerning the antibiotics and the Papanicalaou smear techniques, as well as some replacement of old illustrations, but the former edition has not become out-dated. This book can therefore be commended for use by senior students and practitioners who do not possess a copy of its predecessor.

James Lind: Founder of Nautical Medicine. By Louis H. Roddis; 1951. London: William Heinemann (Medical Books), Limited. 8½″ × 6″, pp. 188, with eight illustrations. Price: 21s.

IN the seventeen-forties James Lind, while serving as a junior surgeon in the Royal Navy, earned posthumous fame as the founder of nautical medicine; and at that early stage of his career his work was characterized by unusual powers of clinical observation, meticulous care in recording his findings, and a consistent urge to employ the scientific method in his medical research. Although he received public acknowledgement during his lifetime as a leading naval physician, an enthusiastic protagonist of much needed reform in naval hygiene and an authoritative writer on the prevention of tropical and deficiency diseases, yet his name has never figured prominently in the medical annals of the past.

With the object of helping to bridge this unfortunate gap in medical biography, Dr. Louis H. Roddis, of the United States Naval Medical Corps, has written a book to commemorate the life and work of Dr. James Lind. He writes fluently and entertainingly of the general scene as Lind was serving his apprenticeship with a well-known surgeon of Edinburgh, before qualifying in 1739 to enter the Royal Navy as surgeon's mate. In the subsequent nine years on active service with the fleet, Lind made an intensive study

of the two formidable "sea diseases", the scurvy and typhus fever or "jail distemper", which had never ceased to be a menace to sailors either in peace or in war. He carried out controlled experiments on his patients to prove that orange and lemon juices were specific remedies for the scurvy, which could be entirely eliminated by including them in the diet as a daily ration.

Unfortunately, the measures recommended by Lind for the prevention of the scurvy, and so clearly stated in the book he published in 1753, went unheeded by the Admiralty for another forty years, although steps were taken earlier to implement his recommendations for the general institution of sanitary precautions to control the high incidence of typhus fever. The final chapters show how Lind used the knowledge gained by these practical experiences as a stepping-stone to higher medical qualifications, which enabled him to practise as a physician in Edinburgh, and then to fill with distinction an important position as chief of the Royal Naval Hospital at Haslar.

A great deal of patient research has gone into the production of this work. Nevertheless, there are a few points which may be called in question by some readers. For instance, Dr. Roddis seems to imply that physicians and surgeons of the eighteenth century were on an equal social footing, whereas there was a deep professional and social gulf between them; and it is far from correct to say that the Monro dynasty of professors at the University of Edinburgh lasted for almost a century.

The book has several illustrations and a brief chronological list of events relative to the general, naval and medical period covered by the text, and it contains the first complete bibliography of Dr. James Lind.

Clinical Interpretation of Laboratory Tests. By Raymond H. Goodale, M.D.; Second Edition; 1952. Philadelphia: F. A. Davis Company. Sydney: Angus and Robertson, Limited. 9½" × 6½", pp. 622, with 107 illustrations, three in colour. Price: 70s.

IN the preface to this book the author names as his object "providing information on the interpretation of laboratory tests and on the most helpful laboratory procedures applicable to the diagnosis of a given disease". The author therefore does not aim at supplanting established texts of clinical pathology, but at providing those who lack the experience of the clinical pathologist with access to the fruits of that experience. It cannot be said that this difficult object has been attained. To provide such a critical survey of laboratory investigation within the compass of one volume would require the greatest economy of treatment. One finds, however, that in Part I in which an effort is indeed maintained to present the subject critically, valuable space is wasted in discussions of normal physiology which are too inadequate to serve any useful purpose and which in any case lie outside the subject. This leaves the author without space in which to discuss such important matters as the meaning of the normal, the meaning of the wide discrepancies reported in regard to many investigations and the fallacies inherent in certain data provided by laboratories.

In Part 2, in which diseases with associated laboratory findings are discussed according to various systems, there is little effort at critical discussion and the subject is presented largely in the form of a series of tabulations, which, however complete, cannot serve any purpose higher than that of a students' *vade mecum*. But the student would be well advised to compile his own *vade mecum* rather than to submit to the authority which unfortunately becomes attached to good printing and binding.

Reaction to Injury: Pathology for Students of Disease: The Reactions of Submission and Adaptation and the Disease Entities Arising out of their Elaboration. By Wiley D. Forbus, M.D.; Volume II; 1952. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 10" × 7½", pp. 1132, with 836 illustrations, 54 in colour. Price: £10 15s.

WITH Virchow's postulate that the cell is the basic unit of disease, great advances in knowledge of pathology were accompanied by a subtle schism by which morphological pathology was regarded as an independent science, taught without reference to other manifestations of disease.

Wiley D. Forbus's book is the most satisfactory attempt yet made to unite the functional and morphological aspects of disease. The second volume of this work appears now, nine years after Volume I was published. The thesis of the work is that the essential element of disease is the reaction of the individual to injury; that the individual can react by resisting, by submitting or by adaptation. The first volume is an introduction to the study of disease and the reactions brought about by resistance to noxious influences. The second volume deals with submission and adaptation to alterations in the body's environment, both external and internal.

This book is therefore concerned with functional pathology in which the clinical, physiological, biochemical and anatomical changes are correlated. The first part of the book deals with submissive reactions by cells and tissues in which degenerations, pigmentations, intoxications and disturbances of circulation are present. Next, manifestations of altered metabolism and structure in systems are discussed. The third section of the book discusses diseases related to growth and development.

The portion of the book dealing with adaptation opens with a discussion of human adaptive processes such as regeneration and healing, and there are sections dealing with the circulatory and the respiratory systems, concluding with adaptive reactions to obstruction of the passage of body fluids from and through the hollow viscera.

Because this book is concerned primarily with function and is not a general textbook of pathology, neoplasms are discussed only from the point of view of the body's reactions to them.

Some subjects are very briefly discussed, and others, usually of lesser importance, are omitted. Yet this is a valuable book. It points the way to true medical wisdom and it should be as valuable in the wards as in the consultant's office.

There are a few errors such as the plate on page 825, which is upside down, so that the legends apply to the wrong figures. The figures and illustrations, some of which are in colour, are of a high order and the double column of print on glossy paper makes for easy reading. The chief drawback, however, is the price.

The Premature Baby. By V. Mary Crosse, O.B.E., M.D. (London), D.P.H., H.M.S.A., D.(Obstet.), R.C.O.G.; Third Edition; 1952. London: J. and A. Churchill, Limited. 8½" × 6", pp. 190, with 18 illustrations. Price: 16s.

THIS book, written by a world authority, may well be recognized as the standard reference work on the premature baby.

Dr. Crosse deals with all aspects of this problem, clearly setting out the important factors in the baby's immediate survival as well as a comprehensive statement on the care and management. The detailed advice given for the conduct of labour is specially valuable as many of the factors militating against the survival of premature babies can be eliminated. She points out the advisability of episiotomy and of a careful forceps extraction in a delayed second stage; protection from infection and chilling is also suitably stressed. The transport of the infant by ambulance in a simple carrier with a supply of oxygen and with adequate heat is described and the need for the skilled attendance of a mothercraft nurse during the journey is pointed out. In addition to these particulars such important matters as the reasons for the transfer to the skilled care and the special facilities of a hospital are set out clearly as well as the opportune time for such transfer.

In the introductory chapters Dr. Crosse emphasizes two facts which all medical practitioners engaged in obstetric or general practice should constantly remember, that prematurity is the greatest single cause of early loss of infant life and that the presence or absence of pathological conditions in the baby or its mother has a definite effect on the development of the baby.

The correlation between the development of the lungs and the maturity of the infant is also noted.

Finally, the author's detailed description with illustrations of the methods of care, management and feeding together with guidance on prevention of infection makes this book invaluable.

Medical Emergencies: Diagnosis and Treatment. By Francis D. Murphy, M.D., F.A.C.P., with a foreword by George Morris Piersol, M.D.; Fourth Edition; 1952. Philadelphia: F. A. Davis Company. Sydney: Angus and Robertson, Limited. 9½" × 6½", pp. 588, with 25 text figures. Price: 80s. 9d.

THIS volume is the fourth edition of Murphy's book previously entitled "Acute Medical Disorders". While there may be some justification for the change in name, this

edition retains much that cannot be included among conditions requiring immediate action. Thus a good deal of material on blood dyscrasias, collagen diseases, liver diseases, tropical diseases and many of the acute infections increases the book's bulk and decreases its usefulness to the resident medical officer or to the general practitioner, both of whom need a small volume on this subject for the pocket or bag.

Nevertheless, as a short work on acute disorders the book is to be commended. Undeniable emergencies are competently described with emphasis on a systematic approach to diagnosis and treatment. A pleasing feature is the author's restraint in his recommendation of therapeutic measures. Obviously only those procedures which he has tried and proved are mentioned, and thus a convincing air of dependability is gained. The style is clear, straightforward and effective.

Acute conditions are dealt with for the most part according to the systems, but there are excellent chapters on coma, convulsions and acute abdominal conditions. Admitting that many acute abdominal emergencies are surgical problems, Professor Murphy points out the responsibility of the general practitioner in diagnosis, and sets out instructions for preoperative and post-operative management. Unfortunately, acute psychiatric disorders like hysteria and mania—also common problems to the general practitioner—are neglected. There is brief mention of epilepsy, but none of *status epilepticus*.

The book concludes with a final chapter on the use of drugs including the antibiotics, ACTH and cortisone. The statement that none of the antibiotics cause agranulocytosis is refuted by recent news that half the deaths from agranulocytosis in the United States of America last year occurred after the exhibition of chloramphenicol.

Primer on Alcoholism. By Marty Mann, with a foreword by T. Ferguson Rodger; 1952. London: Victor Gollancz, Limited. 7½" × 5", pp. 160. Price: 8s. 6d.

THIS book must be read by those who seek to understand alcoholics. Mrs. Marty Mann, the author, herself was an alcoholic who gave up drinking when she joined "Alcoholics Anonymous" in 1936. Since then she has devoted herself to teaching that alcoholism is a disease which can be cured.

Being an ex-alcoholic, she writes of alcoholics as they are. Even though she has no medical degree, she has an extraordinary advantage over non-alcoholic medical writers on alcoholism, in that she writes "from the inside looking out" not "from the outside looking in". As every alcoholic (especially if he is a medical practitioner) knows, most articles on alcoholism lack insight. They describe alcoholism as a moral and psychological problem, not a disease. They make no distinction, as Mrs. Mann does, between the heavy drinker who can control his drinking and the true alcoholic who has no control over it at all. Why this should be is still entirely unknown.

Once it is accepted that the alcoholic is the victim of a disease and does not suffer from defective will power, his character and conduct become comprehensible.

Brilliantly and fluently Mrs. Mann sketches the development of alcoholism from its early stages to its full maturation, with its pathos and tragedy for the patient and for those dear to him.

Whilst chapters are given on treatment, the book is not a text-book on alcoholism. Rather is it an appeal for all to treat the alcoholic as a very sick patient, and not as a social pariah. But above all it must be recommended to the alcoholic himself to read. Therein will he find a vivid description of himself, of his innermost secret thoughts and cunning ways, which he has always regarded as being peculiar to himself alone. And in the midst of his despair (for all alcoholics despair of ever getting well) he will be given the hope that, if he is sincere and honest, he can recover and lead a normal and useful life without alcohol.

The Pathogenesis and Treatment of Thrombosis: With a Clinical and Laboratory Guide to Anticoagulant Therapy. By Irving S. Wright, M.D.; 1952. New York: Grune and Stratton. 9" × 6", pp. 78, with 27 illustrations. Price: $3.00.

THIS slim volume is based on a lecture prepared for the American Heart Association. The author reviews briefly the major aspects of his subject and completes the volume with an appendix setting out the methods used to control the dosage of anticoagulants. Much of the information presented has come from the laboratories of his own medical school and has been published elsewhere. It is of interest that he makes no mention of the use of ethylidene dicoumarin which is now so widely used in Australia. He remarks that patients given antibiotics orally may show an undue fall in prothrombin content when given coumarin compounds, an observation also made in this country by Professor R. D. Wright; it has been attributed to the reduced synthesis of vitamin *K* in the bowel. As a reference for the person anxious to learn about anticoagulant therapy this little volume is adequate.

Surgical Treatment of the Motor-Skeletal System. Supervising editor, Frederic W. Bancroft, A.B., M.D., F.A.C.S., associate editor, Henry C. Marble, A.B., M.D., F.A.C.S.; Second Edition; 1951. Philadelphia, London, Montreal: J. B. Lippincott Company. Sydney: Angus and Robertson, Limited. In two volumes. Part 1: Deformities, Paralytic Disorders, Muscles, Tendons, Bursæ, New Growths, Diseases of Bones and Joints, Amputations. Part 2: Fractures, Dislocations, Sprains, Muscle and Tendon Injuries, Birth Injuries. 10" × 7½", pp. 1300, with 1049 illustrations and three colour plates. Price: £12 18s.

THESE two volumes are the work of 48 American authors, each specially qualified to write on the section allotted to him. The first volume deals with general orthopædics, while the second is devoted to fractures and injuries of joints and muscles. The general aim of the editors has been to produce a practical guide to treatment, and the book is not meant as a work of reference. Primarily concerned with treatment, it includes lengthy discussions on the clinical and diagnostic aspects, and this in fact occupies about half the space.

This general plan has some advantages, but the work of multiple authors is apt to be uneven in quality and emphasis. At times, too, the personal character of each section leads to the exclusion of widely practised methods of treatment —for example, intramedullary nailing, the treatment of congenital dislocation of the hip by means of splints, ischiofemoral arthrodesis and acrylic head arthroplasty.

The set-up of the book leaves something to be desired. The text is in two narrow columns on each page, which makes difficult reading, and does not lend itself to clear headings. Illustrations are frequently small and indistinct, while others might well be omitted, such as the half-page diagram devoted to the operation for subungual hæmatoma. The index, too, could be better prepared. It is unexpected to find leg equalization listed only as a subgroup under "Poliomyelitis".

There is probably no more difficult task in medical literature than to produce a text-book on orthopædic treatment. The subject is vast, and is growing and changing rapidly, so that considerable differences of opinion exist. Such a book, therefore, is received with interest, but is certain to be keenly criticized. This work provides one comprehensive system of treatment, and will be welcomed by those who wish to practise within that system. However, in our opinion such an approach to treatment is too limited to have a wide appeal. Orthopædic, as distinct from occasional surgeons, would prefer a work on a more catholic scale.

The Principles of Nutrition for Practitioners and Students. By C. F. Brockington, M.A., M.D., D.P.H. (Cantab.), with a foreword by J. M. Mackintosh; 1952. London: William Heinemann (Medical Books), Limited. 7½" × 5", pp. 146. Price: 15s.

DOCTORS who are called upon to give lectures in nutrition to social workers, nurses, kindergarten and nursery school teachers will find this little book useful as a reference and they may wish to prescribe it as a text for the students.

It is written with the minimum of technical vocabulary and illustrated by apt and interesting examples. The sections dealing with food rationing and the profession of dietetics are not applicable to Australian conditions. The few pages on family budgeting are interesting and should be used to stimulate Australian dietitians and social workers to develop budgeting standards for this country, a need created by the current high cost of food.

The author has not hesitated to adopt definite requirements for the various nutrients. At the present stage of our nutritional knowledge there is little firm evidence for any set of nutritional requirements for man and the adoption of any figure should be made with reservations. Preceding dietary practices, mechanisms for adaptation to undernutrition and variation between individuals all complicate the simple adoption of a figure for human requirements for the various nutrients. In this book documentation of the evidence on which the various standards are based has been sacrificed for the sake of simplicity. The suggested standards of requirements for nutrients should be used with discretion.

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All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

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Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

GEORGE BASS.

ONE hundred and fifty years ago, on February 5, 1803, George Bass sailed from Port Jackson as master in the brig *Venus* and disappeared. Nothing authentic has been heard of him since. Surgeon, navigator, explorer, naturalist and adventurer, Bass was an adornment to his profession and one of the great men of Australian history. It is strange that a biography of him has been so long in appearing. However, the job has now been done, and done well, by Dr. Keith Bowden of Melbourne, who presents us with all the available knowledge of Bass in a most readable form.[1] The manuscript was awarded first prize in the biography section of the Victorian State Government's Centenary Literary and Historical Competition. The published volume is a credit to author and publisher. Bowden has indeed done a service to his profession and to Australia with this authentic and attractive biography, and we do well to pause a little over its remarkable subject.

George Bass was born in Lincolnshire in 1771, the son and grandson of farmers. When he was six years of age he and his recently widowed mother came to live in the busy shipping port of Boston on the river Witham, four miles from its entry into the Wash. Bass soon felt the call of the sea, and it persisted through grammar school, apprenticeship to the local surgeon and apothecary, walking the London hospitals and qualifying for membership of the Company of Surgeons (the forerunner of the present Royal College of Surgeons of England). In his eighteenth year this dark, handsome six-foot youth qualified as a "surgeon's mate—any rate" in the Royal Navy, and a year later he became a naval surgeon. He served on seven of His Majesty's ships before his appointment in 1794 as surgeon on *H.M.S. Reliance*, which was preparing for a voyage to New South Wales. Besides Bass the ship's company is notable in the light of later events. The master, Captain Henry Waterhouse, became and for the rest of his life remained a good friend to Bass, who in 1800 married his sister. The master's mate was Matthew Flinders, a Lincolnshire doctor's son, who was born only eight miles away from Bass's home; as staunch friends and companions in great deeds, Bass and Flinders are inseparably linked in Australian history. The *Reliance* also carried Captain Hunter, on his way to succeed Phillip as Governor of New South Wales; his experience of Bass during the voyage was the beginning of persistent esteem for this (in Hunter's own words) "ingenious young man". Only seven weeks after their arrival in the colony on September 7, 1795, Bass and Flinders made their first voyage in the *Tom Thumb* when they explored the George's River from its mouth. Then followed for Bass many ventures on land and sea to spy out unexplored country and to search for new or rare specimens. He made a gallant but unsuccessful attempt to cross the Blue Mountains in 1796. He played an important part in the voyage of the *Reliance* to the Cape of Good Hope in 1797, when she brought back to Port Jackson the merinos on which Australia's wool industry was largely founded. He found coal accessible from the sea not many miles south of Botany Bay. Best known are his voyages of exploration: in 1796 he and Flinders in the second *Tom Thumb* explored the Illawarra coast; in 1798 he made his famous voyage in the whale boat as far as Western Port, convincing himself, without proving it finally, that a wide strait separated Van Diemen's Land from New South Wales; in 1798–1799 he was rejoined by Flinders in the *Norfolk* and they circumnavigated Van Diemen's Land. In all this Bass cheerfully accepted great hardship, and, as Bowden points out, "it is all the more meritorious that his magnificent exploratory work was performed during his spare time as ship's surgeon in the *Reliance*". At the same time he was displaying his interest in and intelligent appreciation of natural history, and among Bass's notable contributions in this field Bowden lists his investigations into the anatomy of the wombat, the feeding habits of the swan and the nesting behaviour of the white-capped albatross. On his subsequent commercial voyages, both private and on behalf of the colony, we need not dwell now; Bowden describes them fully. It is enough to say that in them Bass displayed great enterprise, ability and courage in the face of repeated misfortunes. The fateful voyage of 1803 in the *Venus* had as a prime official purpose the obtaining of salted beef and live cattle from the west coast of South America for importation into the colony. This had Governor King's official blessing. Bowden is also convinced—and his arguments make good sense—that Bass unofficially intended to engage in contraband on the South American coast. What happened is not known. From the day the *Venus* cleared Sydney Heads she and her master and crew vanished. Picturesque stories gained currency that Bass was taken prisoner and sent to work in the silver mines of Peru, but their foundation is slight. No real evidence exists that Bass ever reached South America. Bowden makes a masterly survey of the known facts and reasonable inferences, and suggests, as the most likely of

[1] George Bass, 1771-1803: His Discoveries, Romantic Life and Tragic Disappearance", by Keith Macrae Bowden; 1952. Melbourne: Geoffrey Cumberlege, Oxford University Press. 9" × 6", pp. 182, with 12 illustrations. Price: 21s.

various possibilities, that the *Venus* was wrecked off the South Island of New Zealand, where Bass was interested in establishing a fishing industry. Bass at the time of his disappearance was only thirty-two years of age, but "in his short life he had written his name imperishably on the pages of Australian history".

Medicine is jealous of her children and rarely lets them go. Many wander far from her side in search of knowledge, of fame and of the expression of cherished plans and desires. She still claims them though they woo and win their own loves. For John Keats it was poetry, for John Locke philosophy, for Thomas Barnardo philantropy, for David Livingstone the dark heart of Africa, for W. G. Grace cricket, for Bass exploration and high adventure. To his professional work Bass appears to have remained loyal, though it had not been of his own choice that he was educated as a surgeon. His competence has never been questioned, and he enjoyed the confidence of his colleagues in the colony. Victoria quite reasonably claims him as its first doctor, as no medical man had set foot on the territory that was to become Victoria before Bass landed at Western Port in January, 1798. The fact is commemorated by a brass mural in the Medical Society Hall, East Melbourne. Bass was, however, one of those gifted people who, besides being what they are trained to be, can be other things too and be them very well. He was a student and linguist, and also a man of action. An intrepid explorer and skilful navigator, he had eyes for the wonders of plant and animal life. He was as human as he was brilliant, combining vision and great tenacity of purpose with a sense of humour and personal worth that won him many friendships. A contemporary described him as "possessing very great strength of mind, and of a strong, robust habit, fond of enterprise and despising danger in every shape". At the same time he was, in the words of the historian Ernest Scott, "the first man who brought a trained scientific intelligence to bear upon natural phenomena in this country". Governor Hunter said a great deal in simple words when he described Bass to the Home Secretary as "a young man of much ability in various ways out of the line of his profession".

Current Comment.

PRACTICAL HELP FOR THE DISSEMINATED SCLEROSIS PATIENT.

THE National Multiple Sclerosis Society in the United States has produced a series of manuals dealing with the problems of physical medicine and rehabilitation in disseminated sclerosis (as it is usually called in this country). The first manual, which was published in 1951, was designed for medical practitioners. Written by Edward E. Gordon, who is Director of the Institute for the Crippled and Disabled, New York, it is entitled "Multiple Sclerosis: Application of Rehabilitation Techniques". In it Gordon first discusses the possibilities and limitations of rehabilitation procedures, explains in detail the evaluation of disabilities and lays down a programme for rehabilitation with a practical scheme of treatment. A great deal of thought and ingenuity has gone into the details of the scheme, which is not represented as being in any way curative, but is designed to teach the patient how best to live with his disabilities and to exploit residual capacities to the fullest possible extent.

More recently Gordon has prepared four shorter manuals to be put into the hands of patients or those directly caring for them. They apply respectively to four types of patients: independently ambulatory patients, patients ambulatory with aids, wheel-chair patients (these three for the patients themselves) and bed patients (this for those caring for the patient). The material is essentially the same as that in the larger manual for medical practitioners and is designed for use under, and not independently of, medical guidance. The tone of the manuals for patients is encouraging but realistic, and they should appeal particularly to intelligent patients. Nevertheless, their value will depend a good deal on the wisdom and genuine interest of the medical adviser.

Copies of these publications are available free to medical practitioners, if they will advise the manuals appropriate to the needs of their patients. Application should be made to the National Multiple Sclerosis Society, 270 Park Avenue, New York 17, New York, United States of America. This society is active in anything to do with disseminated sclerosis and, while constantly seeking curative or preventive measures, is well aware that no specific has yet appeared. They are doing a notable service in providing these practical aids to patients and their medical advisers, so showing the way to make the best of circumstances that are by no means always ones of unrelieved gloom.

VENTRICULAR FIBRILLATION AND THE STOKES–ADAMS SYNDROME.

THE Stokes-Adams syndrome is traditionally associated with attacks of heart-block, but studies undertaken of recent years have attracted more interest to the occurrence of the typical syncopal and epileptoid attacks during paroxysms of ventricular fibrillation. Elmer S. Robertson and Emmett C. Mathews have published a full account of one such case and have reviewed the literature.[1] Their patient was an elderly man who had suffered an anterior myocardial infarction four months previously, and who was readmitted to hospital for the investigation of syncopal attacks. There he had a prolonged convulsive seizure with arrest of breathing, and the diagnosis of complete heart-block seemed justified. Serial electrocardiograms gave evidence of an anterior myocardial infarction, and as a prophylactic, quinidine sulphate was given in doses of three grains three times daily. The drug was discontinued next day, but the presence of bigeminal rhythm determined its resumption, until after another day of medication frequent syncopal attacks occurred. These seizures lasted three to five minutes and were accompanied by apnœa and cyanosis. The quinidine was again suspended, but the increasing frequency and severity of the attacks led the authors to give the drug by the intravenous route. Tracings showed that the patient had paroxysms of pre-fibrillary tachycardia and of ventricular fibrillation. A dose of 15 grains was given diluted in 300 millilitres of distilled water very slowly and under observation by a direct writing electrocardiograph. Little benefit was noted, and an additional five grains were injected, after which the paroxysms disappeared temporarily. Oral dosage was then resumed, but the patient's condition deteriorated and another intravenous dose was given, with full recognition of the dangers of quinidine administered by this route. The seizures recurred, and the patient died in a paroxysm of ventricular fibrillation; the terminal event was recorded on the electrocardiograph. Autopsy showed advanced arteriosclerosis in the heart, with narrowing of the coronary lumens, and fibrous changes in the myocardium. In retrospect the authors agree that the administration of quinidine aggravated the production of syncopal episodes, and that the apparent improvement during the first injection was due to cardiac depression. During the patient's previous treatment

[1] *Archives of Internal Medicine*, September, 1952.

an electrocardiogram demonstrated the changes of right branch bundle block, and ephedrine was given, and later, after the onset of syncopal seizures, epinephrine. It was thought that these drugs increased the severity of attacks, but had no influence in initiating them. Later tracings had the appearance of those found in bilateral bundle block.

The authors present an analysis of 51 cases from the literature and discuss the whole question. They quote White's warning that treatment should be directed against the fibrillation rather than against the syncopal attacks. Investigations have shown more recently that the circus movement hypothesis is probably without accurate foundation, and that although death may ensue in from six to eight minutes from cerebral anæmia, recovery may follow more frequently than has been thought after a paroxysm. Robertson and Mathews conclude that it is important that the underlying cause of Stokes-Adams attacks should be ascertained by modern methods, and that the association of ventricular arrest with ventricular fibrillation in producing such paroxysms should be realized. The duration of the fibrillation will determine the severity of the cerebral sypmtoms, and as it is likely that more cases will be recognized in the future, the question of treatment is not wholly academic. The authors suggest that it is wise to refrain from using intravenous medication in patients known to have cardiac disease, and to avoid digitalis and quinidine in this respect. In the presence of branch bundle block they advise great caution in the use of quinidine. The question of procedure also arises in the occurrence of ventricular fibrillation during anæsthesia; heroic intracardiac injection has been used with success. Less dramatic is the use of this drug to prevent fibrillation occurring in persons who have a ventricular tachycardia. Finally, Robertson and Mathews suggest that safe procedures in ventricular fibrillation may be the administration of oxygen, the cautious use of coronary dilators such as aminophylline, the cautious use of procaine amide, the injection of dextrose solutions, and the use of potassium chloride. A few other suggestions are also made, but it seems likely that if clinicians diagnose ventricular fibrillation with greater frequency they will at least be very careful what they give and how they give it, and will refrain from the use of quinidine.

THE SPLENIC FLEXURE SYNDROME.

CLINICAL rediscoveries have a distinct value, for memories are short, and the rapid succession of new things sometimes obscures the old. The psychosomatic condition known as "spastic colon" and by other similar names was familiar to physicians of the last generation as one of the syndromes liable to be confused with organic disease; it is, of course, still well known, without perhaps having any name given to it. Certainly it is not uncommon to see persons, usually spare of habit and with some of the stigmata of a sensitive nervous system, who complain of abdominal pain and who have a tender and usually firmly contracted, or at least readily palpable descending colon, and likewise a readily felt abdominal aorta, which has an obviously heaving impulse and is also somewhat tender on pressure. In former days such persons often received unnecessary treatment for constipation; nowadays self-treatment is more likely, inspired by seductive advertisements. It occasionally happens that symptoms arise in other parts of the colon, and when the splenic flexure is the seat of periodic disturbance the diagnosis may not at first be readily made. Hence arises the subject of this note, which is dealt with by T. E. Machella, H. J. Dworken and F. J. Biel in a communication describing what the authors call the "splenic flexure syndrome".[1] They have collected 40 cases, 19 in males and 21 in females. It may be recalled that other types of this colonic syndrome used to be thought more common in women until more careful survey revealed many instances in men. These authors have been particularly interested in the diagnosis of this condition because they found it had been confused with coronary artery disease. The average age of their patients was forty-six years, an age distribution which is possibly somewhat loaded towards the middle age groups because of the special emphasis laid on a possible cardiac lesion. Their patients complained of discomfort in the left upper quadrant of the abdomen as a rule, and also in the precordial area, while a reflection of pain was quite frequently noted in those parts often affected in true coronary disease causing anginal symptoms. The left flank was also the seat of discomfort, but not more commonly than such areas as the chest, the jaw or the arms. The nature of the discomfort varied widely, but a quality resembling fullness or pressure was described both in the left upper abdominal quadrant and in the precordium. In the sites of reference a burning sensation was complained of frequently. The precipitating factors were usually of harmless type, and relief was usually given by the expulsion of flatus. One interesting feature is that the authors made radiological examinations of the abdomens of 15 patients during the periods of discomfort and in each instance could demonstrate an accumulation of gas in the splenic flexure. Barium studies of the whole colon revealed no organic lesion, but in nearly half the patients spasm was reported in the sigmoid or other parts of the colon. Study of films taken after the giving of a barium enema revealed a very sharp angle at the splenic flexure in 32 out of 34 cases; the authors suggest that this may indicate a possible trap for gas. Intubation of the splenic flexure was carried out in nine patients, and inflation with air was found to produce discomfort of a kind similar to that experienced spontaneously. In their summing up the writers state their belief that the syndrome they have studied is a manifestation of spastic colon, a conclusion with which all would surely agree. They also believe that it is of diagnostic importance because it may be confused with disease of the coronary arteries. Investigation of the cardio-vascular state of these patients did not reveal cardiac disease; some of them were referred from a cardiac department for abdominal investigation, but others were actually living in the cautious routines of the cardiac invalid. It may be remarked in conclusion that it is even possible to carry out extensive investigations and yet fail to convince certain patients of the innocence of their symptoms. It is in the earliest stages of the implantation of the cardiac neurosis that prophylaxis has its best opportunity for making somatic treatment unnecessary.

[1] *Annals of Internal Medicine*, September, 1952.

SOCIAL SERVICE AGENCIES IN NEW SOUTH WALES.

THE Council of Social Service of New South Wales has issued a second edition of its "Directory of Social Service Agencies". This is a remarkably comprehensive publication, providing information on the numerous sources in Sydney, government and private, from which help of various kinds can be obtained. It is not merely a list of sources of charity and free assistance, but covers all types of organizations and bodies that play a part in community welfare. The first section deals with Commonwealth and State government and municipal departments and agencies. Then follow sections on health, child and youth welfare, family and adult welfare, service and ex-service personnel and their dependants, seamen, delinquency, recreational and cultural agencies and miscellaneous agencies. The section on health has details of home nursing services, general and special hospitals, agencies for the care of mothers and babies and of the handicapped, and convalescent and holiday homes for adults and for children. Much useful information is included in practically every case. Although most of the agencies mentioned are in Sydney, addresses are provided, so that information and help are available to those in the country. This directory should be in the hands of all general practitioners in New South Wales, and many in specialist practice will find it useful. It is obtainable from the Council of Social Services, Endeavour House, 33 Macquarie Street, Sydney.

Abstracts from Medical Literature.

GYNÆCOLOGY AND OBSTETRICS.

Utero-Vaginal Extirpation for Procidentia.

JAMES V. RICCI AND CHARLES H. THOM (*Am. J. Surg.*, February, 1952) limit the term procidentia to that type and degree of prolapse presenting a protrusion of the entire vagina with a concomitant descent of a cervical stump or of a cervix with uterus. The condition may represent the terminal stage of genital prolapse following obstetrical trauma or congenital weakness of the pelvic supports. It may follow vaginal hysterectomy or total and subtotal abdominal hysterectomy. The authors describe and illustrate the steps in technique of utero-vaginal extirpation for the repair of procidentia in aged and debilitated patients who have passed coital life. Their operative technique comprises the following steps: (i) The anterior vaginal wall is incised, the bladder is displaced upward, the utero-vesical pouch of peritoneum is opened, and the *fundus uteri* is delivered. (ii) The uterine tubes, round ligaments, ovarian ligaments, broad ligaments, uterine vessels and utero-sacral ligaments are clamped, cut and tied on each side. (iii) The posterior vaginal wall is now incised, and the cardinal ligaments are severed near their attachment to the cervix; the lateral vaginal wall is incised by connecting the apex of the anterior vaginal wall incision to the apex of the posterior vaginal wall incision. (iv) The uterus with cervix is now removed, and the stumps of the cardinal ligaments are united in the mid-line. (v) The posterior vaginal wall is separated from the peritoneal sac of the enterocele, and the sac is excised and closed; the incision in the posterior vaginal wall is carried down to the perineum, and the vagina is extirpated by excision of all redundant vaginal wall, anterior and posterior. (vi) The cut edges of the muco-cutaneous line of the vagina are now sutured from the urethro-vaginal region to the region of the perineum, the vagina being thus closed. The operation is completed by a high perineorrhaphy. The authors state that utero-vaginal extirpation is the operation of choice for aged patients past coital life with complete prolapse. The operation is easily and quickly performed, and recurrence is impossible. The operative mortality rate has been nil, and morbidity has been minimal.

Toxæmic Accidental Hæmorrhage.

O'DONEL BROWNE (*J. Obst. & Gynæc. Brit. Emp.*, April, 1952) records a study of 100 patients with toxæmic accidental hæmorrhage treated in the Rotunda Hospital. He defines toxæmic accidental hæmorrhage as bleeding resulting from partial or complete, gradual or sudden, separation of a placenta which is not "prævia" in a women who is twenty-eight weeks (or more) pregnant, and a catheter specimen of whose urine contains albumin either before or after the hæmorrhage. He states that the incidence of this obstetrical emergency at the Rotunda Hospital has remained remarkably constant since 1919 at a figure of 0·5% to 0·9% of total pregnancies. The overall maternal and fœtal loss due to toxæmic accidental hæmorrhage has not decreased despite more extensive and improved antenatal care and prompt admission to hospital. The condition was found to be commonest in *multiparæ*, and the average time of the accident was at the thirty-fourth to thirty-fifth week of gestation. The author draws attention to the high fœtal loss associated with toxæmic accidental hæmorrhage and contrasts this with the lower fœtal mortality rate associated with *placenta prævia*. He considers that this fœtal loss will not be reduced until we know how to detect the minor degrees of placental damage and/or its slight and early separation. Active treatment of early symptoms and signs (phase I) aims at preventing phase II associated with shock. The author's figures suggest that luck rather than pre-natal care governs the fate of the infant, and ante-natal care would also not appear to have been helpful in preventing maternal deaths, as there were seven maternal deaths in the author's series of 100 cases of toxæmic accidental hæmorrhage. The added effect of shock on toxæmia is considered by the author to be a most dangerous event, and the greatest risk appears to be in the toxæmic shock, chronic hypertensive group of patients. Clinical observations such as the effect of the onset of labour, the time interval between the onset of symptoms and the institution of active treatment, changes in blood pressure and the presence of œdema and albuminuria are discussed. The author considers that there are no reliable clinical criteria to indicate how much a placenta has separated or is damaged unless this is sufficient to produce grave constitutional upset in the mother or kill the fœtus *in utero*. Warning signs and symptoms (phase I) are commonly present for some hours or days before the major accident occurs and include crampy abdominal pains, occasional slight vaginal bleeding, irregularity of the fœtal heart, transient albuminuria, abnormal fluctuations of blood pressure and slight temporary shock. The author considers that half-hourly blood pressure records are a valuable guide as to the severity of the case and an aid to treatment. A falling blood pressure associated with a rising pulse rate and a falling pulse pressure is of bad prognostic significance. The author observes that labour rarely commences when the blood pressure is 80 millimetres of mercury, systolic, and 60 millimetres, diastolic, or less, and that efforts to induce labour at this level are not only futile but harmful. He discusses the evolution of treatment for toxæmic accidental hæmorrhage and states that non-recognition of phase I and strongly conservative treatment in phase II have been the general practice at the Rotunda. The importance of early blood transfusion and the role of puncture of the membranes are discussed. The author recommends delivery by lower segment section unless labour begins within an hour or so of restorative treatment followed by puncture of the membranes in phase II cases. He questions the advisability of doing anything more than a lower segment section (for example, Cæsarean hysterectomy) even if the uterus is of the Couvelaire type. He summarizes his views on Cæsarean section in the treatment of toxæmic accidental hæmorrhage as follows: The operation is denied unnecessarily in phase I cases, is usually used too late in phase II cases, should be preceded by early and adequate blood transfusion, and is sufficient without hysterectomy unless uterine rupture is present. In view of the high maternal and fœtal death rates in the past due to toxæmic accidental hæmorrhage, the author recommends that nurses, students and practitioners be taught the seriousness of the complication and the necessity for earlier and more active anti-shock treatment in phase I, and early and adequate blood transfusion combined with improved transport to hospital to prevent phase I passing to phase II. He states that shock having been prevented or treated, the pregnancy should be terminated by earlier Cæsarean delivery in phases I and II.

Accidents Complicating Pelvic Surgery.

LOUIS E. PHANEUF (*New England J. Med.*, July 10, 1952) discusses accidents complicating pelvic surgery in women. He classifies them into immediate or late accidents and into those that occur during abdominal pelvic surgery and those that complicate surgery by the vaginal route. Immediate accidents complicating abdominal section include uretero-vaginal fistula, vesico-vaginal fistula, injuries to the rectum, sigmoid colon and small intestine, and hæmorrhage. The author states that uretero-vaginal fistula usually complicates the radical abdominal pan-hysterectomy for carcinoma of the cervix and may occur directly during the operation, as a result of interference with the blood supply of the ureter during its dissection, or the application of a ligature around the ureter during ligation of the uterine vessels. He considers that the ureter should always be dissected and kept in sight when there is any doubt about its position during a difficult hysterectomy. If either ureter is injured during pelvic surgery it may be treated by anastomosis over a catheter, by side-to-side anastomosis, or by transplantation into the fundus of the bladder, or into the sigmoid colon; or, finally, it may be brought out through the skin in the lumbar region as a temporary measure. Vesico-vaginal fistula is avoided by adequate mobilization of the bladder from the cervix and vagina, care being taken in suturing the vaginal cuff and avoiding interference with the blood supply of the bladder. According to the author the most serious factor in injury to the bladder is the failure to recognize it. He goes on to state that injuries to the bowel, large or small, usually occur during the separation of adherent bowel in the treatment of pelvic endometriosis or chronic pelvic inflammatory disease. Any rent in the bowel should be sutured with or without a temporary enterostomy, or resection of bowel with a suitable anastomosis may be necessary. Hæmorrhage in the pelvis during operation may occur from the ovarian or uterine vessels. The author has not found it necessary to ligate the ovarian artery at its origin at the aorta, but bleeding from a retracted uterine artery may necessitate prompt exposure and ligation of the hypogastric artery at its origin. Late accidents complicating abdominal pelvic surgery include secondary hæmorrhage, pelvic infection, phlebothrombosis and thrombo-embolism, and intestinal obstruction.

These complications are briefly discussed by the author with special reference to preventive measures. The immediate accidents complicating vaginal pelvic surgery are discussed under the headings of urinary fistulæ, recto-vaginal fistula and hæmorrhage. The author considers vesico-vaginal fistula a complication more common after vaginal operations than after abdominal sections. He states that late accidents associated with vaginal plastic surgery include secondary hæmorrhage and infection. Thrombophlebitis, pyæmia and septicæmia rarely occur after vaginal pelvic surgery. Among 1751 consecutive pelvic operations in the author's private practice 21 surgical accidents occurred (1·1%). The urinary bladder was involved in 10 cases, the ureters in four, the small intestine in two and the large intestine in two; perforation of the uterus occurred in one case and infection in two. These cases are briefly reported, and the treatment and results are stated. There were no deaths among these patients with complicating accidents of pelvic surgery.

The Adherent Placenta.

BRYAN WILLIAMS (*J. Obst. & Gynæc. Brit. Emp.*, April, 1952) has reviewed 70 cases of adherent placenta in order to determine the part played by developmental abnormalities of the uterus. He states that an earlier study of the histories of 71 patients with adherent placenta failed to find any constant significant factor in pregnancy, labour, method of delivery or kind of anæsthetic or analgesic used. In most cases the placenta was partly separated, and a cornual implantation of the remaining part was often found. The frequency of cornual implantation in adherent placenta and its occurrence with deformity of the uterus suggested that placental retention might, in some cases, be the result of a developmental abnormality of the uterus. Out of 32 cases of adherent placenta, implantation of the placenta was found in the fundus or cornua in 23, the predominant site being the right cornu. Information is available on the shape of the uterus in 26 cases. Six uteri were normal; there was one double uterus; in five cases the uterus was bicornuate, and in eight cases one cornu was longer or larger than the other. Hysterograms to determine the shape and development of the uterus were performed on 12 patients who had a history of adherent placenta on more than one occasion. Results showed three cases of bicornuate uterus, four of bifid uterus, three in which the right cornu was larger than the left and two of asymmetrical uterine fundi. These 12 patients also had a high incidence of twin pregnancy, abortions and premature labours, malpresentations and dystocia. Thus of 38 cases in which clinical or radiological evidence was available, there was a uterine deformity of some degree in 32. Out of the total of 70 cases there was either a cornual implantation or a uterine deformity or both in 50. The author considers that the high incidence of uterine deformities in patients who develop adherent placenta suggests that a defect of some degree in the fusion of the Müllerian ducts may give rise to a structural and functional disturbance which may not show itself till the third stage of labour and then be an important factor in causing non-detachment of the placenta. He considers that the most important cause of "atonic non-detachment" of the placenta is a developmental deformity of the uterus, commonly of minor degree, with a cornual implantation of at least part of the placenta. If easy expression of the placenta is not successful within one hour of delivery of the child, manual removal of the placenta should be performed.

Basal Narcotics and Eclampsia.

A. U. CAMPBELL AND H. BURTON (*J. Obst. & Gynæc. Brit. Emp.*, February, 1952) review a series of 36 cases of eclampsia in which the convulsions were controlled by "Avertin" and discuss the action and toxic properties of "Avertin", paraldehyde and "Pentothal" with relation to the treatment of eclampsia. They state that prior to 1947 they had used the other well-known hypnotic drugs in an effort to control eclamptic fits. Results were frequently unsuccessful, and chloroform had to be used. Since using rectal "Avertin" therapy, according to the dosage and technique of Dewar and Morris and supplemented with other medical treatment, they have had no maternal death in 36 eclamptic patients and a fœtal mortality rate of 29%. Freshly prepared "Avertin" solution is given rectally to the patient before she is transferred to the flying squad ambulance, and all details of nursing care are followed. The authors favour giving an intravenous injection of hypertonic dextrose solution (20 millilitres of 50% solution) rather than a continuous less concentrated drip administration. Calcium gluconate is also given intravenously daily to protect the liver, and fluid intake and output are controlled. The authors consider that ganglion-blocking drugs and spinal anæsthesia should theoretically have a place in the treatment of eclampsia, but the lowering of blood pressure is not the complete answer to the prevention of eclampsia. Their routine obstetrical treatment includes routine vaginal examination as soon as the "Avertin" has taken effect. If the cervix is "ripe" and the lie longitudinal, the membranes are ruptured. If the cervix is "unripe" and the position is abnormal, Cæsarean section is usually performed. The authors compare their mortality of nil among 36 patients treated in this way with a mortality of six among 36 eclamptic patients treated by a modified Stroganoff method in the four preceding years. Former treatment also resulted in a fœtal mortality of 39%. The authors state that fits recurred in 25% of cases after one dose of "Avertin" and that this is due to inadequate dosage and failure to repeat "Avertin" administration. They consider that "Avertin" treatment reduces the number of spontaneous deliveries and that the operative interference rate is high. Comparative series of cases have not been treated by paraldehyde or "Pentothal", but the action of these drugs is discussed. The authors consider that paraldehyde produces deeper and more prolonged anæsthesia, but has proved disappointing as an anti-convulsant in eclampsia. "Pentothal" has a weaker and shorter anæsthetic action, which can be improved by intravenous drip administration. Obvious disadvantages in this form of treatment are that administration is difficult on "district cases", and skilled medical attention must be constantly available. Patients with impaired renal and hepatic function allegedly do not tolerate normal doses of barbiturates. Other toxic effects of "Avertin" and "Pentothal" are said to be respiratory depression and reduction in blood and cerebro-spinal fluid pressures. Paraldehyde has little, if any, effect on the circulation and respiration. The authors suggest that reduction in blood pressure and cerebro-spinal fluid pressure is the factor which makes the anticonvulsant powers of "Avertin" and "Pentothal" out of all proportion to the depth of anæsthesia that they produce.

Carcinoma of the Cervix.

S. V. WARD, T. B. SELLERS AND J. T. DAVIS (*Am. J. Obst. & Gynec.*, May, 1952) report autopsy findings in 248 patients who died of carcinoma of the cervix and attempt to correlate the causes of death with various factors, aiming at improving treatment. They agree with other workers that death from carcinoma of the cervix is usually the result of uræmia, infection or hæmorrhage rather than cancer cachexia. They state that antibiotics and blood replacement have lowered the mortality due to infection and hæmorrhage, and ureteral obstruction assumes greater importance as a cause of death. They have found that older women with carcinoma of the cervix have a slightly greater tendency to die with obstructed ureters than do younger women. Of the total deaths 51% were due to uræmia and pyelonephritis, 13·7% to hæmorrhage, 11·3% to cachexia and only 3·2% to post-operative or post-irradiation peritonitis. Of the series of patients 60% had ureteral obstruction. The authors found that factors such as parity, stage at which treatment was commenced, symptoms and pathological type did not affect the proportion of patients dying in uræmia. From the available evidence they consider that there may be sufficient time to alleviate ureteral obstruction after the appearance of early signs of its development. Distant metastases were found in 32·9% of autopsy cases, whereas a clinical diagnosis of distant metastases was made in only 14·1% of cases. The most common sites of distant metastases were the lungs, liver, bones and peritoneum. The authors were impressed by unsatisfactory results in attempted relief of pain in advanced growths, despite measures such as prefrontal lobotomy, caudal resection, spinal injection and alcohol injection. In the series 29 patients were treated surgically, and the rather discouraging results are analysed. The authors maintain that radium and X-ray treatment are still the treatments of choice for all carcinomata of the cervix except carcinoma *in situ*. In the latter condition a wide hysterectomy may be in order; and, for those who desire it, initial irradiation treatment followed by wide hysterectomy and gland dissection may be employed for stage I and early stage II growths. The authors do not favour removal of the rectum in radical pelvic surgery unless the rectal wall is involved, but transplantation of the ureters is considered advantageous for block dissection in radical surgery and as a means of prolonging a comfortable life, even when no cure is obtainable.

Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

LI.

FISTULA-IN-ANO.

THE treatment of a fistula-in-ano presents a challenge to the surgeon. The recurrence rate is high, the stay in hospital prolonged, the financial burden heavy, and the penalty of ill-judged surgery sometimes a colostomy.

If the fistula should enter the upper end of the anal canal, the unwary surgeon might divide the ano-rectal ring with disaster to the patient's rectal function; and the proctologist is aware that the fistula which he dreads most, the ano-rectal fistula with an internal opening above the ano-rectal ring, is often the end result of poor surgery. L. E. C. Norbury in a recent Bradshaw lecture reminds us that it is axiomatic amongst proctologists that "more reputations are lost in the treatment of fistula than with any other operation".

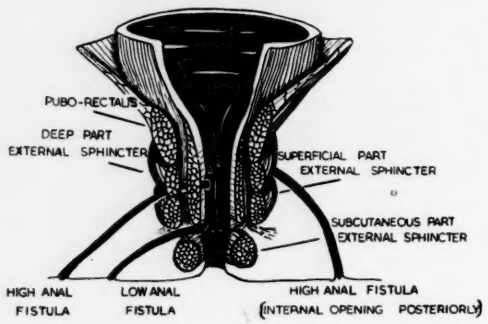


FIGURE I.

Diagram to show the relation of the fistula track (low and high fistula-in-ano) to the various parts of the external sphincter and *levator ani*.

Surgical Anatomy.

Most fistula tracks enter the anal canal just above the subcutaneous portion of the external sphincter; these are known as low-anal fistulæ. The track may pass through the sphincter muscles at a higher level, although remaining below the ano-rectal ring; these are termed high-anal fistulæ and, together with the more common low-anal fistulæ, constitute 90% of all types seen (see Figure I). The sphincter muscle below the ano-rectal ring can be cut with impunity, but the greatest difficulty might be experienced in determining the exact relation of the track to the ano-rectal ring. Fortunately fistulæ which open into the rectum, a variety of ano-rectal fistulæ, are rare.

Surgical Pathology.

Fistulæ-in-ano, in most cases, are the sequelæ of non-specific perianal infections, which often seem to be secondary to mucosal damage caused by a passing fish bone *et cetera*. Suppuration results in an abscess, which either discharges spontaneously or is incised surgically. In many instances a persistent discharging sinus follows, and investigation shows it to be a fistula. The fistula track most commonly enters the anal canal radially opposite the external opening, but sometimes the track curves backwards to enter the anal canal in the mid-line posteriorly (Figure I). Intrasphincteric secondary tracks may leave the main track and travel for a varying distance within the musculature of the sphincter (Figure II). Sometimes a low or high anal fistula on entering the submucous space has a secondary track running upwards —in some cases, well above the ano-rectal ring. The surgeon should remember that these secondary submucosal fistula tracks are more common than primary submucosal fistulæ.

Tracks of fistulæ are lined by granulation tissue; and the surrounding fibrous tissue is usually readily palpable through the skin. There is a sero-purulent discharge from the fistula, which tends to close from time to time; closure is often followed by abscess.

Treatment.

1. *Excision of Fistula.*

Excision of fistula is the standard operation (Figure III, A, B, C, D). Low anal fistulæ actually can be excised; but the term is a misnomer with high anal fistulæ. With the latter the fistula is laid open, and although the unhealthy granulation tissue lining the track is removed, the fibrous tissue covering it is left *in situ*; its excision is unnecessary and dangerous because it takes the operator too close to the ano-rectal ring.

The patient is placed in a lithotomy position. A suitable probe is passed gently along the track into the anal canal. A selection of probes should be available because the tracks vary in diameter. The relation of the probe to the ano-rectal ring is determined, and if the track lies below it the tissues are carefully divided down to the probe, which is consequently released. The vertical edges of the incised wound are cut away to leave a wound as flat as is possible. The granulation tissue of the original fistula track is gently scraped away because any secondary tracks must be detected at this stage. The depths of the wound are carefully trimmed

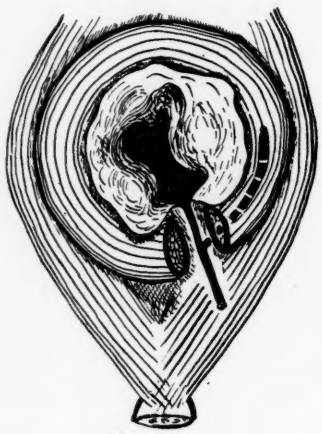


FIGURE II.

Diagram to demonstrate a secondary track branching from the main track.

to leave no potential pockets. Hæmostasis is secured by pressure or by ligatures (3/0 or 4/0 plain cutgut), and a firm dry dressing is applied to the wound.

On the third or fourth post-operative day the dressings are changed; if the patient has a bowel action the dressings come away with the motion, but in other cases a light "Pentothal" anæsthetic can be administered and the dressings changed. Thereafter the dressings are done daily after the bowels have opened. The utmost care is necessary to prevent the wound from losing its flat surfaces and forming a pocket; the resulting residual cavity is the cause of recurrence after the rest of the wound has healed. Seven to ten days after operation granulation tissue begins to cover the wound, and at the end of fourteen days epithelium can be seen growing inwards from the edges to cover the granulations. Daily dressings are still necessary, and dry dressings result in much healthier wounds than do those covered with grease.

The anal portion of the wound is the most difficult to keep under observation. For this reason the surgeon cuts away a considerable amount of perianal skin; this ensures healing of the anal end before the perianal.

This method of treating the common low or high anal fistulæ has several disadvantages. Operation itself takes but a few minutes, but the post-operative treatment is prolonged. It is unwise to discharge the patient from hospital until the wound is covered evenly by granulation tissue and the anal portion has healed; this means at least two or three weeks and sometimes longer in hospital, and it usually takes as long again after the patient's discharge from hospital for

the wound to heal completely. Dressings for the first seven to ten days are uncomfortable for the patient despite the most careful assurance and technique of the surgeon. The fibrosis consequent upon healing of a wound by secondary intention complicates a second operation should it prove necessary.

Some surgeons endeavour to shorten convalescence by applying skin grafts in the post-operative period. These have taken the form of pinch grafts (Gabriel, 1927; Wright, 1934). It means interrupting the ambulatory state of the patient for five or six days, and the "take" is not always very satisfactory because of the poor vascularity caused by the fibrosis under the granulating wound.

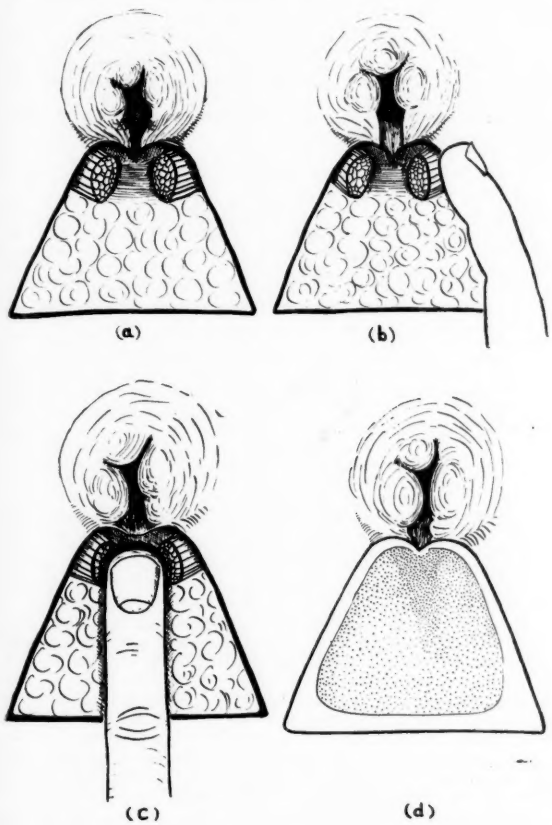


FIGURE III.

The fistula track laid open and allowed to heal by second intention healing. (*a*) The fistula is laid open. (*b*) The wound is kept flat in the post-operative period. (*c*) Particular care is necessary at the anal end of the wound. (*d*) The granulating wound must be kept continuously under observation until the advancing epithelial edges have met.

2. Excision of Fistula and Primary Suture of Wound.

With the advent of chemotherapy and antibiotics an attempt has been made to overcome these disadvantages by suturing the wound (Figure IV). After suitable pre-operative preparation the fistula is excised in the usual way. After the track has been explored for secondary diverticula the wound is carefully sutured. The edges of the wound are not trimmed away because sloping edges are not required. After operation, the bowels are confined for some days. Intensive chemotherapy in the form of penicillin and streptomycin is given.

The big disadvantage of this technique is the danger of hæmatoma formation in the depths of the wound; a contaminated hæmatoma will cause infection and infection a recurrence of the fistula. Moreover, exploration of the wound for secondary tracks is rendered more difficult if the edges of the wound have not been cut away. Horseshoe and semi-horseshoe fistulæ are difficult to treat by this technique.

3. Excision of Fistula and Primary Skin Graft.

The most satisfactory method of treating the low and high anal fistulæ-in-ano is to apply a split skin graft over the wound as soon as the fistula has been excised (Hughes, 1952) (Figure V, A, B, C, D).

The patient is given a preliminary five-day course of succinyl-sulphathiazole (10 grammes daily) and enters hospital the day before operation. The fistula track is laid open, excised and explored, and the edges are trimmed to make the wound as flat as is possible. The edges are made to slope gradually towards the centre, and all ridges and pockets in the floor of the wound are removed with a sharp scalpel. Hæmostasis is secured chiefly by pressure. Very occasionally ligatures of cutgut are required.

A series of guy sutures are placed at intervals around the wound. A thin sheet of skin is cut from the thigh, wrapped over a mould of the wound and placed in position. A strip of cotton wool placed over the anus prevents the skin surfaces of the natal cleft from chafing when the buttocks are strapped together. This is done after the legs are brought down from the lithotomy position.

FIGURE IV.

Excision of the fistula and primary suture.

Penicillin and streptomycin therapy is continued in the post-operative period. There is little pain, but the donor site may be uncomfortable for a day or two. The patient has little trouble in keeping the bowels confined for as long as the surgeon wishes. The graft is inspected on the fifth or sixth day. The guy sutures are removed, and the mould is lifted off the wound. The overlapping edges of the graft are trimmed away, and a piece of cotton wool is placed over the wound. The patient usually has a bowel action on the same day or the next and is then fit for discharge from hospital.

Discussion.

Most fistulæ-in-ano are secondary to a non-specific perianal infection. Very few, if any, heal spontaneously; the attempt, by Nature, to close a tube lined by granulation tissue has been called "third intention" healing (Milligan and Morgan, 1934).

Before the days of chemotherapy the only safe method of treatment was to lay the track open, so that it was converted into a flat wound, and to allow it to heal by secondary intention. The principle is sound and the operative technique relatively simple; but in the post-operative period the surgeon must watch the wound intently to see that it continues to heal by secondary intention and does not revert to third intention healing, as this will result in a pocket, a sinus and recurrence of the fistula. The open wound is painful, requires daily dressing and takes a long time to heal.

Few proctologists favour suture of the fistula wound after excision. The initial fistula was secondary to a non-specific perianal infection; a wound infection after suture must therefore be serious. Deep hæmatomata may harbour organ-

isms for some time before a recurrent abscess develops. In the event of failure the wound must be opened again and converted into a flat wound.

Excision of the fistula with primary skin grafting is a simple technical modification of the long-established method entailing healing by secondary intention. In most cases the surgeon can confidently anticipate a 90% to 100% take. If the patient should complain of pain in the wound post-operatively, it suggests a failed graft; and this may well be secondary to incomplete excision of the fistula track.

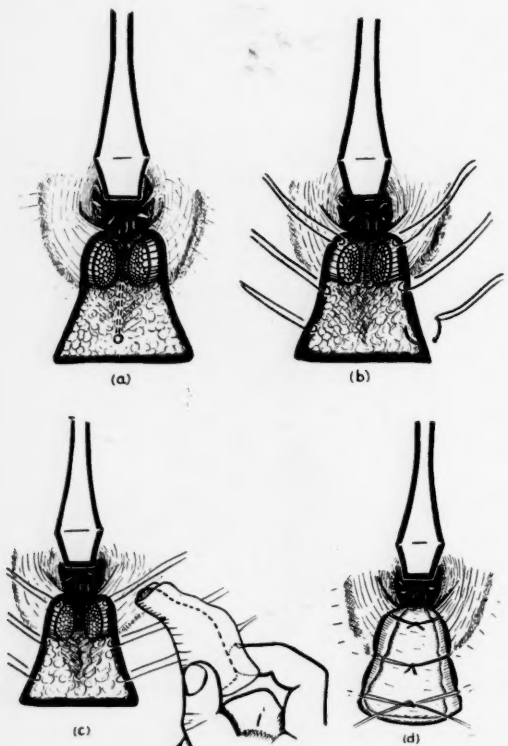


FIGURE V.

Primary skin graft to the wound following excision of the fistula-in-ano. (*a*) The fistula is laid open. (*b*) Guy sutures are inserted around the edge of the wound. (*c*) The graft is wrapped around the face of the mould, which is then inserted into the wound. (*d*) The guy sutures are tied across the back of the wound.

If the graft does not take at all, the surgeon has lost nothing in the attempt; he still has a flat wound, and he can proceed to treat it in the usual way. But the successful case has proved dramatic; the convalescence is greatly reduced. The absence of fibrosis and scarring would certainly favour the surgeon in the event of a second operation becoming necessary.

Summary.

The operations performed for fistula-in-ano are reviewed. The most satisfactory procedure involves an immediate skin graft applied to the raw wound.

Acknowledgement.

I wish to acknowledge gratefully the technical advice generously given by Mr. B. K. Rank, F.R.C.S.

E. S. R. HUGHES,
Melbourne.

References.

GABRIEL, W. B. (1927), "Skin Grafts for Fistulæ", *Proc. Roy. Soc. Med.*, 20: 1278.

HUGHES, E. S. R. (1952), "Primary Skin Graft following Excision of Fistula-in-Ano", *Australian & New Zealand J. Surg.*, 21: 212.

MILLIGAN, E. T. C., and MORGAN, C. NAUNTON (1934), "Surgical Anatomy of the Anal Canal with Special Reference to Ano-rectal Fistulæ", *Lancet*, 2: 1150.

NORBURY, L. E. C. (1949), "Proctology Throughout the Ages", *Ann. Roy. Coll. Surgeons England*, 4: 169.

WRIGHT, R. DOUGLAS (1934-1935), "The Treatment of Anal Fistula", *Australian & New Zealand J. Surg.*, 4: 169.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held at the Women's Hospital, Melbourne, on April 2, 1952. The meeting took the form of clinical demonstrations by members of the medical and surgical staff of the hospital.

Pregnancy After Tubal Reconstruction.

DR. J. W. JOHNSTONE showed a series of six patients from the sterility clinic in whom pregnancy had occurred after implantation of the Fallopian tubes into the uterus. It was explained that in all the cases the blockage was at the cornual end adjacent to the uterus and the operation was in a class quite distinct from the usual one of salpingostomy or salpingolysis. In that type of case it was commonly assumed that the prognosis was almost hopeless and operative reconstruction was not worth while. The series of patients was presented to give some contradiction to that opinion. Points in technique were illustrated by a colour film of the operation, and another film on case 333 showed the delivery by Cæsarean section of the first child after the implantation operation.

In case 476 the patient had been sterile for over two years, and an abortion had occurred seven years before. The Fallopian tubes were obstructed at the uterine end. Rubin's test had been performed six times and salpingograms had been prepared three times. The husband was fertile and the endometrium secretory. Tubal implantation was performed in November, 1950, and the patient had had amenorrhœa since the middle of December, 1951. The results of pregnancy tests were positive, showing the patient at the time of the meeting to be three months pregnant.

In case 1135 the patient had been operated upon in July, 1950, and at the time of the meeting was only three weeks from term. Gas tests after implantation showed a free passage into the peritoneal cavity.

The patient in case 1236 was shown with her baby, aged six months. Operation had been performed in October, 1949, and premature vaginal delivery took place in August, 1951.

The patient in case 257 was present with two boys delivered spontaneously in June, 1949, and January, 1951, the operation having been performed in May, 1947.

The patient in case 333 also had two boys, each having been delivered by Cæsarean section in September, 1948, and August, 1951. The implantation operation had been performed in April, 1947.

The history and photographs of the patient in case 1300 were shown without the patient. Tubal implantation had been performed in July, 1950, and amenorrhœa commenced in December, 1950. The pregnancy proved to be in the interstitial part of the tubal implant, and terminated by spontaneous premature vaginal delivery of a stillborn infant at thirty-two weeks of gestation. Intraperitoneal rupture with hæmorrhage from the placental site took place simultaneously and the uterus had to be removed.

In commenting on the cases Dr. Johnstone said that a marriage was considered absolutely sterile when there was complete azoospermia, persistent anovulation or complete tubal block. Of patients presenting with sterility of not less than two years' duration, about 20% were found to have no passage through the tubes. As about 8% of the married population were involuntarily sterile, the problem of reconstruction of the tubes was of consequence to gynæcologists. Dr. Johnstone said that in his experience blocked tubes could be divided into three classes: those which were completely disorganized, those blocked at the fimbriated end, which was usually dilated, and those which were blocked in the narrow part near the uterus. Operation was not justified on the patients with disorganized tubes.

cuff salpingostomy could be performed in patients with hydrosalpinx, and the operation of choice in the third group was implantation of the outer ends of the tubes, after their division distal to the blockage, into a new opening in the uterus. The Müllerian duct had a great natural propensity to restore the continuity of its lumen if given the chance. Preliminary tubal tests with gas and with radio-opaque injection and X-ray examination were necessary, and the possibility of isthmical spasm and errors in the investigations should be remembered. In all the cases discussed the site of blockage was demonstrated at operation by retrograde insufflation with a syringe and special cannula. Genital tuberculosis should be excluded as far as possible by endometrial biopsy. The operation was not without disadvantages, as was shown by case 1300, in which the patient lost both her baby and the uterus from irregular implantation. Nevertheless, those present at the meeting could see five very healthy children before them, as well as two other expectant mothers. That represented the result of 26 operations of the implantation type, and thus a reasonable measure of success could be promised to a group of otherwise hopeless women.

VICTORIAN BRANCH NEWS.

Section of Preventive Medicine.

A MEETING of the Section of Preventive Medicine of the Victorian Branch of the British Medical Association will be held in the Medical Society Hall, 426 Albert Street, East Melbourne, at 4.30 p.m. on Thursday, February 12, 1953. Sir Allen Daley, who recently retired from the position of Chief Medical Officer to the London County Council, is visiting Australia under the auspices of the Nuffield Foundation and will give an address on the "Health of the Nation". All members of the Branch are invited to be present.

NEW SOUTH WALES BRANCH NEWS.

Section of Pædiatrics.

THE following is the programme for 1953 of the Section of Pædiatrics of the New South Wales Branch of the British Medical Association. Unless otherwise stated, the place of meeting is the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney, and the time 8.30 p.m.

February 10: "The Management of Common Difficulties in Infancy", Dr. Clifton Walker.

April 14: "Squint", Sir Norman Gregg.

May 12, at 8 p.m.: Clinical meeting at the Royal Alexandra Hospital for Children; patients to be presented by members of the resident medical staff.

June 9: "Burns", Dr. J. Steigrad and Dr. E. S. Stuckey.

August 11: "The Diagnosis of Intracranial Tumours in Childhood", Dr. L. Rail and Dr. M. S. Schreiber.

September 29, at 3 p.m.: Clinical meeting at the Spastic Centre, Mosman.

October 13: "The Cerebro-Spinal Fluid Changes and the Treatment of the Meningitides", Dr. Alison Garven and Dr. J. W. Beveridge.

All members of the medical profession who are interested are invited.

Medical Societies.

MELBOURNE PÆDIATRIC SOCIETY.

THE monthly meeting of the Melbourne Pædiatric Society was held at the Children's Hospital, Melbourne, on Wednesday, September 10, 1952.

The meeting was the first "H. Douglas Stephens Memorial Meeting" to be held annually as a tribute to the late Dr. Henry Douglas Stephens.

DR. REGINALD WEBSTER gave an address on the life of the late Dr. Stephens. This was published in the issue of September 20, 1952, at page 419.

Osteopetrosis (Marble Bones).

DR. ROBERT SOUTHBY stated that he had never been an advocate for the presentation to the Society of rare clinical conditions or "oddities" and felt that an explanation was necessary for the case he was about to present, that of an infant with all the characteristics of osteopetrosis or "marble bones". The occurrence of this condition in infants especially was exceedingly rare and the hospital records contained no example of such a condition, nor had such a patient been presented previously at a clinical meeting at the Children's Hospital.

Dr. Southby said that his excuse for presenting the patient under such circumstances was that she attended the hospital for one of the reasons for which babies most frequently were brought for treatment, namely, snuffling, failure to thrive and pallor. She had the following case history. C.N., born on March 16, 1952, apparently a normal full-time female infant, whose birth weight was seven pounds five ounces, was breast fed for the first nine weeks but progressed slowly. She was first examined at hospital at the age of ten weeks with the history that she had been "snuffly" since birth, seemed "blocked up" in the nose, was always grunting and had some difficulty in breathing. On the day of admission to hospital she had vomited after each feeding. The stools had always been constipated. She presented as a pale baby with a free discharge of clear mucus from the nostrils blocking the nasal airway and causing mouth breathing and constant grunting. The head was large, with a circumference of fifteen and three-quarter inches, a large, fontanelle, widened sutures and prominent eyes. The abdominal wall was lax and protuberant, and the liver and spleen were each palpable for two fingers' breadth below the respective costal margins. In addition optic atrophy and severe anæmia were present.

Dr. Southby said that it was of some interest to mention that the infant was admitted with the provisional diagnosis of "failure to thrive query cretinism", and on admission to the ward was regarded as having a possible congenital syphilitic infection. On seeing the child for the first time, Dr. Southby considered that she was most likely suffering from gargoylism, for, in addition to the features already mentioned, she had very thick gum margins, especially of the upper jaw. The diagnosis was made, as apparently frequently happened with this condition, when the report from the radiologist was received. The radiological report from Dr. H. G. Hiller was as follows:

> There is dense hypercalcification of all the bones of the body of this infant, particularly all the shafts of the long bones including those of the hands and feet, as well as the ribs, pelvic and shoulder girdles, vertebræ and the base of the skull. They show amorphous structure with lack of differentiation into cortex, medullary cavity and spongy bone. The base of the skull shows the individual bones as dense amorphous masses, although normal in size and shape, except for the small pituitary fossa with thickened posterior clinoid processes. The width of the sutures particularly at the base suggests hydrocephalus which may be present in some forms of osteopetrosis in infants. Some evidence of rickets is present in the early films, and in those taken one month later there is definite healing of this condition and in addition a "cloak" of new bone at all the growing ends, as well as enveloping the bones of the pelvis and scapulæ.

Dr. Southby quoted the following results of investigations.

On May 30, 1952, the hæmoglobin value was 10·2 grammes (70%). Nucleated red blood cells totalled 42,400 per cubic millimetre. The red blood cells showed marked anisocytosis and poikilocytosis, and polychromasia with numerous stippled red cells. Culture of a swabbing from the throat yielded *Staphylococcus aureus* which was sensitive only to streptomycin and aureomycin.

On June 4 the red blood cells numbered 2,630,000 per cubic millimetre. The bleeding time was three minutes and the clotting time four minutes. The platelets numbered 120,000 per cubic millimetre.

On June 16 a blood transfusion of six ounces was given.

On June 25 the hæmoglobin value was 8·4 grammes (58%). The red blood cells numbered 2,800,000 per cubic millimetre. Numerous stippled cells were present, and the nucleated red cells were of varying degrees of maturity.

On July 16 the hæmoglobin value was 6·8 grammes (47%). Ninety nucleated red cells per hundred white corpuscles were found. Many stippled cells were present.

On July 30 a blood transfusion of eight ounces was given.

Dr. Southby then demonstrated the infant herself, and in addition a series of clinical photographs and skiagrams.

DR. E. E. PRICE mentioned that osteopetrosis was thought to be allied to Ollier's disease and the osteochondrodystrophies, and was apparently the result of a defect in the development of the osteo-skeleton from the chondro-skeleton. Mr. Price asked whether this opinion was still the commonly accepted one.

DR. ELIZABETH MCCOMAS, in reply to Mr. Price, said that this opinion was still held.

DR. JOHN COLEBATCH said that osteopetrosis was rare in Australia compared to Europe and America. Possibly over the next few decades an increase in the incidence of the disease in Australia would be seen. The condition usually resulted in extramedullary hæmatopoiesis. Dr. Colebatch then asked whether the parathyroid glands were associated with the development of the disorder and whether parathormone had any place in treatment.

Dr. Southby, in reply, said that there was some evidence, from literature on the disorder, that the parathyroid glands were involved, but the results of parathormone treatment were unconvincing. Dr. Southby then inquired if, in view of the hæmatological findings, there was any evidence for a relationship with lead poisoning.

DR. ALAN WILLIAMS, in reply to Dr. Southby, said that he was unable to answer the question, but certainly the hæmatological findings of the two conditions bore a resemblance to each other. However, a similar hæmatological appearance was found in most cases of myelophthisic anæmia.

DR. P. CODY mentioned that Albright, by using graded doses of parathormone experimentally, was able to produce all varieties of bone disorders from osteoporosis and *osteitis fibrosa cystica* to osteopetrosis.

Imperforate Rectum: A New Surgical Technique.

MR. F. DOUGLAS STEPHENS read a paper entitled "Imperforate Rectum: A New Surgical Technique Based on the Study of Pathological Anatomy". In introducing the subject, he said that congenital deformities of the hind gut fell into two main groups. The first consisted of the deformities of the anus, in which the rectum above was well developed. Those were more common and more simply treated, and had a much better prognosis. That group was not to be discussed. The second consisted of rectal deformities, in which there was absence of a large segment of rectum.

Mr. Stephens said that many studies had been made on the visceral anomalies, but few, if any, had correlated the corresponding abnormalities of the pelvic floor and sacrum. The sphincters and the *levator ani* musculature had been examined in the normal subject and in the patient with these rectal anomalies, and the findings were to be presented. On the basis of the pathological anatomy of the sphincter mechanism available, a new surgical procedure had been fashioned to reconstruct the anal canal.

Mr. Stephens said that he wished to thank Mr. Denis Browne for his great help and for providing the wealth of material which had made the study possible.

Anatomy of the Pelvis: Normal.

Describing the normal anatomy of the pelvis, Mr. Stephens said that in the newborn infant the level of the pelvic organs was constant. A line drawn from the upper surface of the pubis to the sacro-coccygeal junction, the pubo-coccygeal line, demarcated the level of the lower margin of the bladder neck, the pelvic peritoneal pouch and Houston's third fold of the rectum. The verumontanum and the origin of the *levator ani* were situated immediately below it. In the female the pouch of Douglas was more frequently on the level of the line, but more rarely it was considerably higher or lower. The line represented an important embryological level. In the male it represented the upper limit of that part of the rectum which was formed from the subdivision of the cloaca. The Wolffian and Müllerian ducts gained attachment to the uro-genital sinus at approximately that level. In the female the Müllerian ducts migrated from that level down the posterior wall of the uro-genital sinus and opened externally independently in the vestibule.

Anatomy of the Pelvis in Imperforate Rectum.

Turning to the anatomy of the pelvis in imperforate rectum, Mr. Stephens said that the deformity was caused by failure of subdivision of the primitive cloaca. The cloaca then conveyed the genito-urinary and alimentary contents to the exterior. The terminal end of the rectum, in the male, was situated at the upper level of the undivided cloaca, which was at or above the pubo-coccygeal line. In the female, owing to the migration of the vaginal bulbs in a caudal direction, the rectum was carried distally and finally opened at a variable level into the posterior wall of the vagina as a recto-vaginal fistula. The two special types of imperforate rectum deformities to be discussed were the recto-urethral fistula and recto-vaginal fistula.

Anatomy of the Sphincters.

The internal and external sphincters developed in relation to the proctodeal pit or that part of the rectum formed from the ectoderm. In the deformity under discussion the proctodeal pit was very rudimentary or absent. The external sphincter was correspondingly rudimentary, developing as a thin, sagittal velum of voluntary muscle gaining attachment to the under surface of the raphe which extended from the perineal body to the coccyx and being inserted into the anal dimple. It was not possible to utilize this thin collection of voluntary muscle fibres in reconstructive surgery. As the visceral component was absent, there was no intrinsic internal sphincter.

The normal *levator ani* muscle arose from the pubis and side wall of the pelvis along the white line of Waldeyer and the ischial spine. That was slightly below the pubo-coccygeal line. The anterior fibres formed the pubo-rectalis sling and were inserted into the rectum at the line of the anal valves. The more posterior fibres were inserted into the central raphe and coccyx, forming the pelvic diaphragm.

The *levator ani* in the deformity was well formed, though modified to the visceral components which perforated the diaphragm—namely, in the male the cloacal canal or urethra, and in the female the urethra and vagina. The visceral sling component of the *levator ani* in the male was formed around the cloaca on a slightly higher plane than the normal pubo-rectalis. This sling was situated immediately under the recto-urethral fistula. In the female this sling formed in relation to the vagina and recto-vaginal fistula.

Clinical and Radiological Diagnosis of the Imperforate Rectum.

Mr. Stephens said that in the male the imperforate rectum must be diagnosed radiologically. Accurate centring of the film in the lateral view was essential to record the exact level of the terminal gut. The centre of the true pelvis was situated on the level of the upper surface of the greater trochanter of the femur. The Wangensteen and Rice method of inversion radiology was used in the newborn period. By contrast the gas-filled rectum was apparent against the solid structures of the pelvis. Inversion of the child was essential to allow the gas in the colon and rectum to rise and displace the meconium. There were numerous important details in the technique and pitfalls in the interpretation of the skiagrams for the discussion of which there was insufficient time. For older children with colostomies, a lipiodol technique was required.

In the common form of imperforate rectum in the male the terminal end of the gut could be distinguished by radiology, lying on or slightly below the pubo-coccygeal line as demarcated on the skiagrams. In the female the fistula into the vagina could be examined directly with the naked eye in the anæsthetized child. Inversion skiagrams in the presence of wide fistulæ were unreliable owing to the free escape of the contrast gases from the gut. Skiagrams were unnecessary in diagnosing the visceral anomaly, but were required to determine the state of development of the sacrum.

Deformities of the Sacrum.

In a considerable number of cases of imperforate rectum deformity there were deficiencies in the coccyx and the lower sacral vertebræ. Deficiencies involving the last two sacral vertebræ were compatible with a fairly well-formed *levator ani*. Deficiencies of the lower three might be associated with a very thinned-out *levator ani* musculature. Involvement of the lowest four sacral vertebræ appeared to be incompatible with any useful *levator ani* musculature. Apparently, absence of the second and third sacral vertebræ indicated absence or deficiency of these segmental somites and their accompanying nerves. Colostomy would appear to be the best form of treatment for such cases.

Surgical Technique.

Mr. Stephens went on to say that, having diagnosed the absence of a *levator ani* musculature, it was incumbent on the surgeon to put it to the best possible advantage with the least damage in relation to the new anal canal. A midline incision was made over the terminal end of the sacrum and coccyx, and the sacro-coccygeal joint was then disarticulated. The visceral deformity was then cleared in the supralevator space, and the fistula was detached from the urethra or vagina, the deficiency in this being immediately repaired. The sling of the *levator ani* was situated caudal to the fistula and was difficult to visualize through the exposure, but it was preserved from harm by passing the jaws of a right-angled forceps towards the perineum in a direction parallel and close to the urethra in the male or the vagina in the female. The skin of the perineum in the site intended for the new anus was raised up by the pressure of the beaks of the forceps, and an elipse of skin was removed. The forceps then became visible in the perineum; a piece of tape was grasped by the jaws of the forceps in the perineum and was withdrawn back along the course of the forceps, which were removed from the supralevator space through the original incision. The tape was thus threaded up through the floor of the pelvis within the sling-like sphincter component of the *levator ani*, and by traction on both ends of the tape, the sling could be gently enlarged in a backward direction.

It had been found that the hind gut in cases of imperforate rectum in which the lowest limit of gut descended to or below the pubo-coccygeal line could be mobilized sufficiently through the supralevator space to permit anastomosis of gut to the skin of the perineum without tension. The terminal gut having been mobilized sufficiently, it only remained to guide it accurately through the enlarged muscular sling of the levator and sew it to the skin at the site of the new anus.

Mr. Stephens said that the perineal approach to the deformity was inclined to harm the fibres of the sphincter-like muscle of the levator. The abdomino-perineal method could direct the new anal canal through the levator musculature in its non-sphincteric diaphragm behind the sling-like component. The method described had the advantages of ensuring minimal harm and maximal sphincteric action of this important muscle.

Mr. Stephens summarized his paper in the following terms. (i) Recto-urethral and recto-vaginal fistulæ were two forms of imperforate rectum. In each deformity a definite segment of rectum was deficient. (ii) The pubo-coccygeal line helped to differentiate rectal from anal abnormalities radiologically. (iii) The *levator ani* was the sole sphincter mechanism available for reconstructive surgery. That muscle was deficient in gross abnormalities of the sacrum involving absence or gross lesions of the second and third sacral segments, which were apparently the segments from which the levator muscles and their nerves were derived. (iv) The sacro-coccygeal approach which was used in the surgical technique of the reconstruction operation preserved the sphincter component of the *levator ani*.

Mr. Stephens concluded by expressing his gratitude to the surgeons of the Hospital for Sick Children, Great Ormond Street, London, for their help, and to Dr. Martin Bodian, of the same hospital, and Dr. J. W. Perry, of the Melbourne Children's Hospital, for providing him with material from their respective departments of pathology. Part of his work had been done with the assistance of grants from the Nuffield Foundation.

MR. J. G. WHITTAKER, in opening the discussion on Mr. Stephen's paper, remarked that after many years he still appeared to be sitting at the feet of the Stephens family. The paper presented by Mr. F. Douglas Stephens was the result of painstaking research, and was essentially practical. The conception of using the pubo-rectalis as a sling and sphincter was a most valuable contribution to the surgery of imperforate rectum.

MR. W. R. FORSTER stated that he had formed the opinion that the position of the gas bubble was an unreliable radiological sign. If the rectum was blocked with meconium, an inaccurate estimation of the site of termination of the rectum was obtained. Mr. Forster asked Mr. Stephens whether a patient suffering from an imperforate rectum required immediate surgery or whether it was safe to wait for two to three days before surgery was attempted. Mr. Forster went on to say that on the occasions on which the rectum terminated high up in the pelvis near the pelvic brim, it appeared that a perineal approach was impracticable.

Mr. Stephens, in reply, said that if the gas bubbles were high in the abdomen with the baby in the inverted position, and did not reveal a sharp caudal outline, the baby should be radiologically examined again twenty-four or thirty-six hours later. Frequently gas did not reach the caudal extremity until some abdominal distension had developed. The infants affected seldom died in the first twenty-four hours unless an associated abnormality such as renal aplasia was present. There was no immediate urgency for surgery, and one could safely wait for one to two days. Mr. Stephens said that on the occasions on which the bowel ended above the pubo-coccygeal line, it was impossible to bring the rectum down sufficiently with a perineal approach because of the great tension involved. The operation then had to be performed in two stages. The first stage was division of the inferior mesenteric artery and vein, with a delay to permit the development of an anastomotic circulation. Following this procedure, mobilization of the bowel was simplified, and the rectum could be brought to the surface in the perineum. Mr. Stephens said that he had not performed this procedure.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

THE QUARANTINE STATION AT MORETON BAY.[1]

Colonial Secretary's Office,
Sydney,
11 October, 1850.

The Medical Adviser to the Government,
Parramatta.

Sir,

I do myself the honor to inform you that in consequence of the death of Dr. Ballow who had charge of the Quarantine Station at Moreton Bay where the emigrants by the "Emigrant" are in quarantine the Police Magistrate at Brisbane and Dr. Mallon the present medical Superintendent have requested that another medical man may be engaged. I am therefore directed by His Excellency the Governor to request that you will nominate some properly qualified medical practitioner for this Service and state the remuneration which should be paid to him. The Police Magistrate has applied to the medical men in the District—those in the immediate neighbourhood have declined proceeding to the Quarantine Station but from some at a distance no answer had been received.

I have, &c.,
E. DEAS THOMSON.

Obituary.

CHARLES HALLILEY KELLAWAY.

AUSTRALIA today has a position in the field of medical research and education that is very high in relation to its human resources. The development of that repute in the world of medical science has been due to many people, but the one man whose influence on the process was outstanding was Charles Kellaway. In 1923 he succeeded Patterson as Director of the Walter and Eliza Hall Institute in Melbourne. At that time the Institute was little more than a set of clinical laboratories attached to the Melbourne Hospital. A start had been made to define some of the medical problems requiring investigation in Melbourne, but neither in Melbourne nor elsewhere in Australia was there work in progress which had any serious impact on the progress of medicine. When Kellaway left the Institute after twenty-one years' service he had brought it to adult stature. It occupied new and adequate buildings and it was well known throughout the world. In a record unique for any similar institution in the British Commonwealth it had five Fellows of the Royal Society (Kellaway, Fairley, Cameron, Feldberg and Burnet) amongst past or present members of its staff. More importantly the development of the Institute and

[1] From the original in the Mitchell Library, Sydney.

Kellaway's personal qualities were together a potent stimulus to other centres in Australia, both in the universities and in relation to the teaching hospitals, to develop comparable facilities for research in medicine and the basic medical sciences. Charles Kellaway had many other claims to the affection and respect of those who knew him, but this was the major, the unique contribution to Australia for which his memory must always be honoured by our profession.

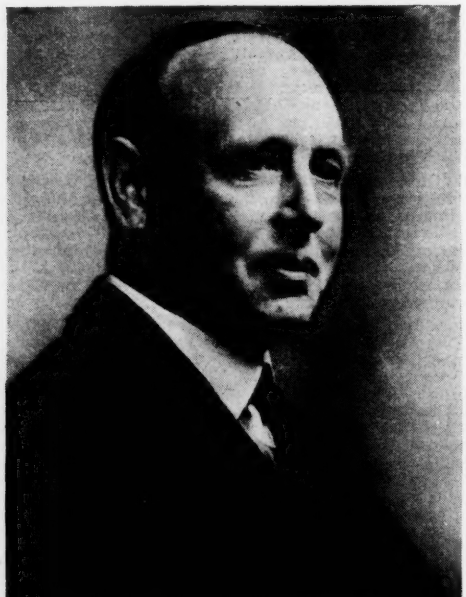
Charles Halliley Kellaway was born in Melbourne on January 16, 1889, the son of Reverend A. C. Kellaway, at that time curate of the Saint James's Old Cathedral in West Melbourne. He was educated at Melbourne Grammar School and entered on his medical course at the University of Melbourne in 1906 with the intention of becoming a medical missionary—there was a strong tradition of missionary work in his family. He graduated M.B., B.S. in 1911 and took his M.D. in 1913 and M.S. in 1915. He had done a brilliant undergraduate course and for a time was uncertain of the field in which he should seek his life work. He was attracted almost equally to physiology, surgery and anatomy, and in 1915 he held an acting professorship in anatomy at the University of Adelaide. This, however, was only a temporary appointment accepted to help overcome the difficulties associated with the outbreak of World War I.

Soon he was on active service, his first appointment being to Number 3 Australian General Hospital to work with Lieutenant-Colonel C. J. Martin on bacillary dysentery. He went to France in 1917 and served as regimental medical officer to the 13th Battalion until May, 1918. He was awarded the Military Cross for conspicuous gallantry and devotion to duty after the battle of Zonnebeke, September 26, 1917. "He worked for more than 24 hours without a moment's respite dealing with the wounded from 5 other battalions in addition to his own, as well as controlling the work of his stretcher bearers." In May, 1918, he was called to join the newly formed Medical Research Committee in England for physiological research into the human problems of military aviation. His first work was on the influence of anoxæmia on the functioning of the adrenal glands and similar topics. At this period he worked at the Lister Institute and came under the lasting influence of H. H. Dale (now Sir Henry Dale, O.M.). When the war was over he collaborated with Dale in a classic study of anaphylaxis and anaphylatoxins and realized that he had found his real career as an experimental physiologist. In 1919 he came to Australia for a brief period as acting professor of physiology in Adelaide, but on his appointment as Foulerton Student of the Royal Society he returned to England to work at University College Hospital Medical School.

The Walter and Eliza Hall Institute had been planned in 1914 and Dr. G. C. Mathison, killed on Gallipoli in 1915, named as director. Buildings were erected in 1916, but the Institute began to function only in 1920 under the directorship of Dr. S. W. Patterson. Early in 1923 Dr. Patterson resigned to take up an English appointment and in September, 1923, Kellaway was invited to succeed him. Within a year or two the general pattern of how the Institute was to develop under his guidance was becoming clear. On a much smaller scale it was to be modelled on the Lister Institute or the National Institute for Medical Research at Hampstead (that Dale and Douglas were then bringing into full activity). Kellaway envisaged three research groups, in physiology, biochemistry and bacteriology, to be in close association with the hospital pathologist and clinical biochemist, but each to be free to follow its own lines of research. It took some years for this to be accomplished. The income of the Institute in 1923 was almost limited to the £2800 *per annum* provided by the Walter and Eliza Hall Trust and for the next fourteen years one of the main preoccupations of the director was to find money from any available source to allow the Institute's normal development. At times it was an almost heart-breaking task.

It is not fitting that a first class scientist should have to go cap in hand for small sums wherever he could find them. Any other man I think would have given up the struggle and returned to work in England where he had both an excellent scientific reputation and influential friends. But Charles Kellaway was a good Australian, his roots were in Melbourne and his ruling ambition was to bring the Institute to full European or American status. He was always optimistic and he was making new friends all the time. That was his great strength. Everyone liked Kellaway. He might seek an introduction to some potential benefactor with nothing in mind but money for the Institute, but almost invariably he would end by bringing that benefactor into his circle of personal friends. There was no hypocrisy whatever in his make-up; he liked people and only a most exceptional person could fail to reciprocate. Steadily there came increasing support from all sorts of sources. Each year the budget was a little larger, members of the staff came and went, but the trend was always toward larger numbers. More papers appeared from the Institute and the work was of better quality. Kellaway himself found a fertile new field in the study of the pharmacology of Australian snake venoms which led him into what was probably his best scientific work on the nature of tissue damage by toxic agents.

In 1937 the Commonwealth Government established the National Health and Medical Research Council, and Kellaway could feel a new assurance of support by the community both for his own Institute and more important still, for the wider development of medical research in Australia. When World War II broke out in 1939 the Hall Institute had an established position in the world of science, important new work was appearing in the pharmacology of tissue injury, in the nature of virus disease and in the chemistry of hæmoglobin and its derivatives. Through the generosity of public and private sources a large new building for the Institute was being constructed with the new Melbourne Hospital, and Kellaway could feel that his primary ambition had been fully realized.



The war, of course, brought major changes. Kellaway had never completely severed his military connexions, and from 1923 to 1936 had served as Army Director of Hygiene in Victoria. Soon after the outbreak of the war he was appointed Director of Pathology at Army Headquarters, Melbourne, and immediately threw himself into the task of staffing and equipping the pathological services for the second Australian Imperial Force. It was his responsibility also to guide the organization of blood transfusion services, A B O typing of service men, and all the practical problems of organizing collection and storage of blood. He soon collected a first-rate team, Wood, Ross, Miss Williams and Red Cross workers, led by Dr. Lucy Bryce, and turned over much of the Institute's laboratory space to this work. When the situation became potentially disastrous for Australia with the entry of Japan into the war, Kellaway was recalled for more important duties as scientific consultant to the medical branches of all the armed services. With the decision to produce armoured fighting vehicles in Australia, many physiological problems arose, and in 1941-1942 he spent several months in England and the United States on such studies. Later he directed research in Australia on the problems of tank crews operating in tropical climates. His opinions were sought on all medical-scientific matters arising

in the Pacific theatres of war, and as scientist turned consultant and administrator he had much opportunity for the exercise of his genius for friendship and his skill in human relationships. He met everyone that mattered and left an army of friends in England and America.

At the end of 1943 the Wellcome Foundation decided to appoint a scientific director to have overall control of research policy in the great Anglo-American complex of pharmaceutical factories, serum laboratories and research centres that had been built up by Sir Henry Wellcome. Kellaway was the obvious man for the post. The invitation was sent to him by Sir Henry Dale, and after some hard thinking he accepted. He realized that the post was wholly an administrative one and that he would make no further contributions to experimental science. In most ways it was a unique situation for a scientist. The Wellcome Foundation holds all the shares of Burroughs Wellcome and Company, and is charged both to maintain the commercial success of the firm and to utilize all distributable profits for the support of research in medical science. At this distance it is hard to assess Kellaway's success in the very difficult task of guiding research policy in six established units so that a satisfactory balance should be struck between fundamental work and research needed to ensure the economic stability of the company in a highly competitive field. What one can be certain of is that the Wellcome laboratories continue to flourish, that a fine new chemical centre has been established at Beckenham, and that as elsewhere Kellaway had the affection and respect of all those with whom he had to deal.

Kellaway died in harness. In November, 1951, he was planning a long-desired short visit to Australia. An acute illness led to examinations that disclosed an incurable condition. For ten months he carried on with his work with the utmost courage. He did not allow his increasing weakness even to interfere with his summer fishing holiday, but the end could not be indefinitely delayed and he died on December 12, 1952, aged sixty-three years.

This is not the place to attempt more than a brief assessment of Kellaway's scientific work. In the history of physiology he will probably be remembered as one of those who extended into new fields the techniques and ideas of the greatest physiologist-pharmacologist of our time, H. H. Dale. The work with Fairley and others on the Australian snake venoms will remain a classic. It was the most comprehensive study ever made of a group of animal poisons. On the one hand he showed the striking peripheral action of colubrid venoms on nervous mechanisms, their curari-like effect on the motor end-plates, paralytic action on sensory nerve endings and direct action on muscle as contrasted with their relatively slight influence on the central nervous system. His major interest, however, was on their circulatory effects and in particular on how far these were secondary to the liberation of histamine from cells damaged by venom. This interest in the part played by histamine in toxic and traumatic conditions was a central theme of Kellaway's work. In addition to snake venoms, bacterial toxins, and antigens in anaphylactically sensitized animals, he showed with various collaborators that heat, light in the presence of photosensitizers, and some anæsthetics liberated histamine from damaged tissues. For a time he was inclined to attribute much of the pharmacological effect of such agents to the histamine liberated, but as the work developed he found that other active agents were also concerned. Much work was done on a "slowly reacting substance" not yet characterized except by its action on smooth muscle *in vitro* and on cardiodepressant agents related to adenyllic acid. Proteins and enzymes, too, were found to be liberated into the perfusion fluid from organs damaged by one or other agent. At the present time the exact contribution of histamine to the pathology of "shock" states in man is not clear. Almost certainly it is only one component of a very complex situation.

Two interesting side activities to the snake venom work had immunological bearings. One was concerned with the classic problem of the snake's immunity to its own venom. Here his conclusion was that this was a combination of intrinsic insusceptibility *plus* the presence in the tissues of detoxicating enzymes. There was no evidence of antibody being involved. The second was in relation to tissue immunity. This was shown to be an artifact due simply to the segregation in the tissue spaces of normal circulating antibody.

Kellaway became a Fellow of the Royal Society in 1940, an honour that he particularly cherished. He was a member of the council from 1947 to 1949. In 1937 he was invited to give the Dohme Lectures at Johns Hopkins University when he dealt with his work on snake venoms. In 1948 he gave the Sharpey-Schafer lecture in Edinburgh.

Any formal account of a great man's life must necessarily be made up mainly of his public activities, his published work and his influence on his own professional field. There remains unexpressed the essence of his personality. Others were closer to Charles Kellaway than I was and could find better words to express his charm, his kindliness, his enthusiasm for the task in hand, his delight in mock pedantry and his nice choice of German epithets to describe an unsatisfactory experiment. He was my "boss" for twenty years, and like every one of his juniors, I had many occasions to appreciate his tolerance, his generosity and his power to smooth over human difficulties. Outside the laboratory he had his hobbies—in the nineteen-twenties bird photography, in the thirties trout fishing—and his family. No one who knew Charles Kellaway in Australia will ever think of him without also recalling his wife. They were both people of outstanding personality with an easy cheerfulness and friendliness that made entry into their home a delight. Our deepest sympathy goes to Mrs. Kellaway and their three sons.

F. M. BURNET.

Bibliography of C. H. Kellaway.[1]

MARTIN, C. J., KELLAWAY, C. H., and WILLIAMS, F. E. (1918), "Epitome of the Results of the Examination of the Stools of 422 Cases Admitted to No. 3 Australian General Hospital, Cairo, for Dysentery and Diarrhœa; March to August, 1916", *J. Roy. Army M. Corps*, 30 : 101.

KELLAWAY, C. H. (1919), "The Effects of Diminished Tension of Oxygen, with Especial Reference to the Activity of the Adrenal Glands", Medical Research Committee, London, Special Report 37.

KELLAWAY, C. H. (1919), "Some Physiological Effects of Anoxæmia", Proceedings of the Physiological Society, *J. Physiol.*, 52 : 63, 1919.

KELLAWAY, C. H. (1919-1920), "The Hyperglycæmia of Asphyxia and the Part Played therein by the Suprarenals", *J. Physiol.*, 53 : 211.

KELLAWAY, C. H. (1921), "The Effect of Certain Dietary Deficiencies on the Suprarenal Glands", *Proc. Roy. Soc.*, ser. B, 92 : 6.

KELLAWAY, C. H. (1921-1922), "The Toxicity of the Blood of Adrenalectomised Frogs", *J. Pharmacol & Exper. Therap.*, 18 : 399.

KELLAWAY, C. H., and COWELL, S. J. (1922), "Non-Specific Desensitisation", *Brit. J. Exper. Path.*, 3 : 268.

DALE, H. H., and KELLAWAY, C. H. (1922), "Anaphylaxis and Anaphylatoxins", *Phil. Trans. Roy. Soc. B.*, 211 : 273.

KELLAWAY, C. H., and COWELL, S. J. (1923), "On the Concentration of the Blood and the Effects of Histamine in Adrenal Insufficiency", *J. Physiol.*, 57 : 82.

KELLAWAY, C. H., and HUGHES, T. A. (1923), "Observations on the Influence of Insulin on Normal Metabolism in Man", *Brit. M. J.*, 1 : 710.

KELLAWAY, C. H., and COWELL, S. J. (1923), "Spontaneous Desensitisation", *Brit. J. Exper. Path.*, 4 : 255.

BOYCOTT, A. E. and KELLAWAY, C. H. (1924), Compensatory Hypertrophy of the Suprarenals", *J. Path & Bact.*, 27 : 171.

BRYCE, L. M., KELLAWAY, C. H., and WILLIAMS, F. E. (1924), "A Study of Hydatid Antigen", *Australian J. Exper. Biol & M. Sc.*, 1 : 77.

DEW, H. R., KELLAWAY, C. H., and WILLIAMS, F. E. (1925), "The Intradermal Reaction in Hydatid Disease and its Clinical Value", *M. J. Australia*, 1 : 1.

KELLAWAY, C. H. (1925), "The Utility of the Casoni Reaction in the Diagnosis of Hydatid Disease", *M. J. Australia*, 1 : 3.

DAVIES, G. F. S., KELLAWAY, C. H., and WILLIAMS, F. E. (1925), "A Study in Organ Specificity", *Australian J. Exper. Biol. & M. Sc.*, 2 : 117.

KELLAWAY, C. H., DAVIES, G. F. S., and WILLIAMS, F. E. (1923), "The Source of the Protein in the Albuminuria of Experimental Nephritis", *Australian J. Exper. Biol. & M. Sc.*, 2 : 139.

KELLAWAY, C. H., BROWN, C. J. O., and WILLIAMS, F. E. (1926), "Paths of Renal Infection", *Brit. J. Exper. Path.*, 7 : 337.

CAMERON, G. R., and KELLAWAY, C. H. (1927), "Compensatory Renal Hypertrophy", *Australian J. Exper. Biol. & M. Sc.*, 4 : 155.

KELLAWAY, C. H., BROWN, C. J. O., and WILLIAMS, F. E. (1927), "Ascending Renal Infection", *M. J. Australia* Supplement, September 17 and 24, page 1.

KELLAWAY, C. H., and WILLIAMS, F. E. (1927), "Specific Localization of Streptococci", *M. J. Australia*, 2 : 269.

KELLAWAY, C. H. (1927), "Diagnostic Tests in Hydatid Disease", *M. J. Australia* Supplement, November 19, page 1.

KELLAWAY, C. H. (1928), "The Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne", *M. J. Australia*, 2 : 702.

KELLAWAY, C. H. (1928), "Hydatid Fluid as an Anaphylactic Antigen", *J. Path. & Bact.*, 31 : 141.

KELLAWAY, C. H., FAIRLEY, N. H., and WILLIAMS, F. E. (1928), "The Filterability of Hydatid Antigens", *Australian J. Exper. Biol. & M. Sc.*, 5 : 189.

KELLAWAY, C. H. (1928), "Anaphylactic Experiments with Extracts of Liver Fluke (Fasciola Hepatica)", *Australian J. Exper. Biol. & M. Sc.*, 5 : 273.

[1] I am indebted to Miss F. E. Williams and Miss Mary Cook for their help with the bibliography.—F.M.B.

KELLAWAY, C. H. (1929), "Some Bacteriological Aspects of Apical Infection in its Relation to General Disease", *M. J. Australia*, 1: 235.

KELLAWAY, C. H. (1929), "Anaphylactic Studies with Extracts of Hydatid Scolices", *Brit. J. Exper. Path.*, 10: 115.

KELLAWAY, C. H. (1929), "Symposium on Snake Bite: The Venom of Notechis Scutatus", *M. J. Australia*, 1: 46.

KELLAWAY, C. H. (1929), "Symposium on Snake Bite: A Preliminary Note on the Venom of the Australian Copper-Head (Denisonia Superba): Its Toxic Effects in the Common Laboratory Animals", *M. J. Australia*, 1: 56.

KELLAWAY, C. H. (1929), "Symposium on Snake Bite: A Preliminary Note on the Venom of Pseudiches Guttatus", *M. J. Australia*, 1: 64.

KELLAWAY, C. H. (1929), "Symposium on Snake Bite: Observations on the Certainly Lethal Dose of the Venom of the Death Adder (Ancanthophis Antarcticus) for the Common Laboratory Animals", *M. J. Australia*, 1: 87.

KELLAWAY, C. H. (1929), "Symposium on Snake Bite: The Action of the Venoms of the Copperhead (Denisonia Superba) and of the Death Adder (Ancanthophis Antarcticus) on the Coagulation of the Blood", *M. J. Australia*, 1: 97.

KELLAWAY, C. H. (1929), "The Action of the Australian Snake Venoms on Plain Muscle", *Brit. J. Exper. Path.*, 10: 281.

KELLAWAY, C. H., and WILLIAMS, F. E. (1929), "The Venoms of Oxyuranus Maclennani and Pseudechis Scutellatus", *Australian J. Exper. Biol. & M. Sc.*, 6: 155, 1929.

KELLAWAY, C. H., FREEMAN, M., and WILLIAMS, F. E. (1929), "The Fractionation of Australian Snake Venoms. I. The Venom of the Death Adder (Ancanthophis Antarcticus)", *Australian J. Exper. Biol. & M. Sc.*, 6: 245.

KELLAWAY, C. H., and EADES, T. (1929), "Field Notes on the Common Australian Venomous Snakes", *M. J. Australia*, 2: 249.

KELLAWAY, C. H. (1930), "The Specificity of Active Immunity Against Snake Venoms", *J. Path. & Bact.*, 33: 157.

KELLAWAY, C. H. (1930), "Observations on the Certainly Lethal Dose of the Venom of the Black Snake (Pseudechis Porphyriacus) for the Common Laboratory Animals", *M. J. Australia*, 2: 3.

KELLAWAY, C. H., and THOMSON, D. F. (1930), "Observations on the Venom of a Large Australian Snake, Pseudechis Australis (Gray)", *Australian J. Exper. Biol. & M. Sc.*, 7: 134.

KELLAWAY, C. H. (1930), "Local Venesection in the Treatment of Snakebite of the Limbs", *M. J. Australia*, 1: 2.

KELLAWAY, C. H. (1930), "The Venom of Latrodectus Hasseltii", *M. J. Australia*, 1: 41.

KELLAWAY, C. H. (1930), "The Anaphylactic Reaction of the Isolated Uterus of the Rat", *Brit. J. Exper. Path.*, 11: 72.

BURNET, F. M., and KELLAWAY, C. H. (1930), "Recent Work on Staphylococcal Toxins, with Special Reference to the Interpretation of the Bundaberg Fatalities", *M. J. Australia*, 2: 2.

KELLAWAY, C. H., PENROSE, J. S., and SOUTHWOOD, E. (1930), "On the Incidence of Certain Diseases in the Domestic Herbivora in Victoria", Commonwealth of Australia, Department of Health.

KELLAWAY, C. H., BURNET, F. M., and WILLIAMS, F. E. (1930), "The Pharmacological Action of the Exotoxin of Staphylococcus Aureus", *J. Path. & Bact.*, 33: 889.

KELLAWAY, C. H. (1930), "Local Venesection in the Treatment of Snake Bite: An Experimental Study", *M. J. Australia*, 2: 351.

KELLAWAY, C. H., and WILLIAMS, F. E. (1931), "The Serological and Blood Relationships of Some Common Australian Snakes", *Australian J. Exper. Biol. & M. Sc.*, 8: 123.

KELLAWAY, C. H. (1931), "Observations on the Certainly Lethal Dose of the Venom of the Common Brown Snake (Demansia Textilis) for the Common Laboratory Animals", *M. J. Australia*, 2: 747.

KELLAWAY, C. H., and MORGAN, F. G. (1931), "The Treatment of Snake Bite in Australia", *M. J. Australia*, 2: 482.

KELLAWAY, C. H. (1931), "Snake Venoms and Antitoxic Immunity", *M. J. Australia*, 2: 3.

KELLAWAY, C. H. (1931), "The Immunity of Australian Snakes to Their Own Venoms", Mathison Lecture. *M. J. Australia*, 2: 15.

FREEMAN, M., HOLDEN, H. F., LEMPRIERE, W. W., SCOTT, R. K., WILLIAMS, F. E., and KELLAWAY, C. H. (1931), "Some Observations on the Bendien Test for Cancer", *M. J. Australia*, 2: 778.

KELLAWAY, C. H., and WILLIAMS, F. E. (1932), "Some Observations on Cellular Immunity to Snake Venom", *J. Path. & Bact.*, 35: 193.

KELLAWAY, C. H., and FAIRLEY, K. D. (1932), "The Clinical Significance of Laboratory Tests in the Diagnosis of Hydatid Disease", *M. J. Australia*, 1: 340.

KELLAWAY, C. H. (1932), "Some Observations on Coramine", *Melbourne Hosp. Clin. Rep.*, 3: 3.

KELLAWAY, C. H., and HOLDEN, H. F. (1932), "The Peripheral Action of the Australian Snake Venoms. I. The Curari-Like Action on Frogs", *Australian J. Exper. Biol. & M. Sc.*, 10: 167.

KELLAWAY, C. H., CHERRY, R. O., and WILLIAMS, F. E. (1932), The Peripheral Action of the Australian Snake Venoms. II. The Curari-Like Action in Mammals", *Australian J. Exper. Biol. & M. Sc.*, 10: 181.

KELLAWAY, C. H. (1932), "The Peripheral Action of the Australian Snake Venoms. III. The Reversibility of the Curari-Like Action", *Australian J. Exper. Biol. & M. Sc.*, 10: 195.

BURNET, F. M., KELLAWAY, C. H., and WILLIAMS, F. E. (1932), "Cellular Immunity and Antibody in the Tissue Spaces", *J. Path. & Bact.*, 35: 199.

KELLAWAY, C. H., and THOMPSON, D. F. (1932), "Observations on the Venom of a Melanotic Insular Variety of the Tiger Snake (Notechis Scutatus)", *Australian J. Exper. Biol. & M. Sc.*, 10: 35.

KELLAWAY, C. H. (1932), "Venomous Land Snakes in Australia", *Bull. Antivenin Inst. Amer.*, 5: 53.

KELLAWAY, C. H., and WILLIAMS, F. E. (1933), "The Investigation of the Toxicity and Sterility of a Commercial Preparation Containing Modified Snake Venom", *M. J. Australia*, 1: 581.

KELLAWAY, C. H. (1933), "Snake Venoms as Muscular Poisons", Presidential Address. *Aust. N.Z. Assoc. Adv. Sc.*, Section N, 21: 370.

KELLAWAY, C. H. (1933), "Some Peculiarities of Australian Snake Venoms", *Tr. Roy. Soc. Trop. Med. & Hyg.*, 27: 9.

KELLAWAY, C. H., and WILLIAMS, F. E. (1933), "Hæmolysis by Australian Snake Venoms. I. The Comparative Hæmolytic Power of Australian Snake Venoms", *Australian J. Exp. Biol. & M. Sc.*, 11: 75.

KELLAWAY, C. H., and WILLIAMS, F. E. (1933), "Hæmolysis by Australian Snake Venoms. II. Some Peculiarities in the Behaviour of the Hæmolysis of Australian Snake Venom", *Australian J. Exper. Biol. & M. Sc.*, 11: 81.

KELLAWAY, C. H. (1934), "A Note on the Venom of the Sydney Funnel-Web Spider, Atrax Robustus", *M. J. Australia*, 1: 678.

KELLAWAY, C. H. (1934), "The Venoms of Some of the Small and Rare Australian Venomous Snakes", *M. J. Australia*, 2: 74.

KELLAWAY, C. H. (1934), "The Venoms of the Broad-Headed Snake (Hoplocephalus Bungaroides) and of the Yellow-Banded Snake (Hoplocephalus Stephensi)", *M. J. Australia*, 2: 249.

FREEMAN, M., and KELLAWAY, C. H. (1934), "The Venom Yields of Common Australian Poisonous Snakes in Captivity", *M. J. Australia*, 2: 373.

KELLAWAY, C. H. (1934), "The Venom of the Ornamented Snake Denisonia Maculata", *Australian J. Exper. Biol. & M. Sc.*, 12: 47.

KELLAWAY, C. H. (1934), "The Peripheral Action of Australian Snake Venoms. IV. Action on Sensory Nerve Endings in Frogs", *Australian J. Exper. Biol. & M. Sc.*, 12: 177.

KELLAWAY, C. H., and WILLIAMS, F. E. (1934), "The Sterilization of Catgut", *Australian & New Zealand J. Surg.*, 4: 118.

KELLAWAY, C. H., and WILLIAMS, F. E. (1935), "Antigenic Differences Between the Venoms of the Tiger Snake Notechis Scutatus and the Black Tiger Snake Notechis Scutatus var. Niger", *Australian J. Exper. Biol. & M. Sc.*, 13: 17.

KELLAWAY, C. H. (1935), "Mussel Poisoning", *M. J. Australia*, 1: 399.

KELLAWAY, C. H. (1935), "The Action of Mussel Poison on the Nervous System", *Australian J. Exper. Biol. & M. Sc.*, 13: 79.

KELLAWAY, C. H. (1935), "Some Recent Studies on Intestinal Obstruction". *Australian & New Zealand J. Surg.*, 4: 384.

KELLAWAY, C. H., and LEMESSURIER, D. H. (1935), "The Venom of the Platypus (Ornithorhynchus Anatimus)", *Australian J. Exper. Biol. & M. Sc.*, 13: 205.

KELLAWAY, C. H., and LEMESSURIER, D. H. (1936), "The Vaso-Depressant Action of the Venom of the Australian Copperhead (Denisonia Superba)", *Australian J. Exper. Biol. & M. Sc.*, 14: 57.

KELLAWAY, C. H. (1936), "Some Reflections on the Sterility of Surgical Catgut and on Allied Matters", *Roy. Melbourne Hosp. Clin. Rep.*, 7: 1.

FELDBERG, W., and KELLAWAY, C. H. (1937), "Liberation of Histamine from the Perfused Lung by Snake Venoms", *J. Physiol.*, 90: 257.

FELDBERG, W., and KELLAWAY, C. H. (1937), "Liberation of Histamine from the Perfused Lung of the Guinea-Pig by Bee Venom", Proceedings of the Physiological Society, *J. Physiol.*, 91: 2.

FELDBERG, W., and KELLAWAY, C. H. (1937), "Circulatory and Pulmonary Effects of the Venom of the Australian Copperhead (Denisonia Superba)", *Australian J. Exper. Biol. & M. Sc.*, 15: 81.

KELLAWAY, C. H. (1937), "The Results of the Excision of the Venom Glands of the Australian Tiger Snake (Notechis Scutatus)", *Australian J. Exper. Biol. & M. Sc.*, 15: 121.

FELDBERG, W., and KELLAWAY, C. H. (1937), "Circulatory Effects of the Venom of the Indian Cobra (Naia Naia) in Cats", *Australian J. Exper. Biol. & M. Sc.*, 15: 159.

FELDBERG, W., and KELLAWAY, C. H. ((1937), "Cirrculatory Effects of the Venom of the Indian Cobra (Naia Naia) in Dogs", *Australian J. Exper. Biol. & M. Sc.*, 15: 441.

FELDBERG, W., and KELLAWAY, C. H. (1937), "Liberation of Histamine and its Role in the Symptomatology of Bee Venom Poisoning", *Australian J. Exper. Biol. & M. Sc.*, 15: 461.

KELLAWAY, C. H. (1937), "Snake Venoms. I. Their Constitution and Therapeutic Applications", *Bull. Johns Hopkins Hosp.*, 60: 1.

KELLAWAY, C. H. (1937), "Snake Venoms. II. Their Peripheral Action", *Bull. Johns Hopkins Hosp.*, 60: 18.

KELLAWAY, C. H. (1937), "Snake Venoms. III. Immunity", *Bull. Johns Hopkins Hosp.*, 60: 159.

KELLAWAY, C. H. (1938), "The Sir Richard Stawell Oration", *M. J. Australia*, 1: 365.

FELDBERG, W., and KELLAWAY, C. H. (1938), "Liberation of Histamine and Formation of Lysocithin-Like Substances by Cobra Venom", *J. Physiol.*, 94: 187.

FELDBERG, W., and KELLAWAY, C. H. (1938), "Liberation of Histamine by Staphylococcal Toxin and Mercuric Chloride", *Australian J. Exper. Biol. & M. Sc.*, 16: 249.

KELLAWAY, C. H., HOLDEN, H. F., and TRETHEWIE, E. R. (1938), "Tissue Injury by Radiant Energy and the Liberation of Histamine", *Australian J. Exper. Biol. & M. Sc.*, 16: 331.

FELDBERG, W., HOLDEN, H. F., and KELLAWAY, C. H. (1938), "The Formation of Hysocithin and of Muscle-Stimulating Substance by Snake Venoms", *J. Physiol.*, 94: 232.

KELLAWAY, C. H. (1938), "Cellular Response to Injury". The Bancroft Memorial Lecture. *M. J. Australia*, 2: 447.

KELLAWAY, C. H. (1938), "The Symptomatology and Treatment of the Bites of Australian Snakes", *M. J. Australia*, 2: 585.

KELLAWAY, C. H. (1939), "Twenty-Five Years of Progress in Medical Research", *M. J. Australia*, 2: 18.

KELLAWAY, C. H. (1939), "Animal Poisons", *Ann. Rev. Biochem.*, 8: 541.

KELLAWAY, C. H., and TRETHEWIE, E. R. (1939), "Photodynamic Action and the Liberation of Histamine", *Australian J. Exper. Biol. & M. Sc.*, 17: 61.

KELLAWAY, C. H., and TRETHEWIE, E. R. (1939), "Tissue Injury by Volatile and Gaseous Anæsthetics", *Australian J. Exper. Biol. & M. Sc.*, 17: 225.

KELLAWAY, C. H., and TRETHEWIE, E. R. (1940), "The Liberation of a Slow-Reacting Smooth Muscle-Stimulating Substance in Anaphylaxis", *Quart. J. Exper. Physiol.*, 30: 121.

KELLAWAY, C. H., and TRETHEWIE, E. R. (1940), "The Liberation of Adenyl Compounds from Perfused Organs by Cobra Venom", *Australian J. Exper. Biol. & M. Sc.*, 18: 63.

KELLAWAY, C. H., TRETHEWIE, E. R., and TURNER, A. W. (1940), "Neurotoxic and Circulatory Effects of the Toxin of Cl. Welchii Type D", *Australian J. Exper. Biol. & M. Sc.*, 18: 225.

KELLAWAY, C. H., TRETHEWIE, E. R., and TURNER, A. W. (1940), "The Liberation of Histamine and of Adenyl Compounds by the Toxin of Cl. Welchii Type D", *Australian J. Exper. Biol. & M. Sc.*, 18: 253.

KELLAWAY, C. H., and TRETHEWIE,, E. R. (1940), "A Note on the Extraction of Adenyl Compounds from Tissues", *Australian J. Exper. Biol. & M. Sc.*, 18: 265.

KELLAWAY, C. H., and TRETHEWIE, E. R. (1941), "Tissue Injury by the Toxin of Cl. Welchii Type A", *Australian J. Exper. Biol. & M. Sc.*, 19: 17.

KELLAWAY, C. H., and TRETHEWIE, E. R. (1941), "The Injury of Tissue Cells and the Liberation of Pharmacologically Active Substances by the Toxins of Cl. Welchii Types B and C", *Australian J. Exper. Biol. & M. Sc.*, 19: 77.

KELLAWAY, C. H., GEID, G., and TRETHEWIE, E. R. (1941), "Circulatory and Other Effects of the Toxin of Cl. Septique", *Australian J. Exper. Biol. & M. Sc.*, 19: 297.

KELLAWAY, C. H., and RAWLINSON, W. A. (1944), "Studies on Tissue Injury by Heat. I. The Influence of Anoxia", *Australian J. Exper. Biol. & M. Sc.*, 22: 63.

RAWLINSON, W. A., and KELLAWAY, C. H. (1944), "Studies on Tissue Injury by Heat. II. The Liberation of Enzymes from the Perfused Liver", *Australian J. Exper. Biol. & M. Sc.*, 22: 69.

KELLAWAY, C. H., and RAWLINSON, W. A. (1944), "Studies on Tissue Injury by Heat. III. Isolated Limb Preparations", *Australian J. Exper. Biol. & M. Sc.*, 22: 83.

KELLAWAY, C. H. (1947), "Perfusion Experiment in Study of Tissue Injury". Sharpey-Schafer Memorial Lecture, *Edinburgh M. J.*, 54: 333.

KELLAWAY, C. H. (1948), "The Wellcome Research Institution", *Proc. Roy. Soc.* A 193: 435, B 135: 259.

Corrigendum.

AIR VICE-MARSHAL E. A. DALEY has advised us of an error in his paper, "Medical Standards of Fitness in the Royal Australian Air Force", which was published in the issue of January 10, 1953. On page 26, column 2, line 40, the phrase "2·25 prism dioptres" should read "*plus* 2·25 D sphere".

Deaths.

THE following death has been announced:

FOSTER.—George William Foster, on December 19, 1952, at Natimuk, Victoria.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JANUARY 3, 1953.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.[2]	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.[3]
Acute Rheumatism	..	..	..	..	..	..	..	..	..
Amœbiasis	..	2	..	..	..	..	..	..	2
Ancylostomiasis	..	..	..	..	..	..	..	..	..
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	1(1)	..	..	..	1
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	2(2)	..	17(15)	..	..	..	2	..	21
Diphtheria	8(2)	5(3)	3	..	4(3)	..	..	1	21
Dysentery (Bacillary)	..	1(1)	..	..	1(1)	..	..	..	2
Encephalitis	1	2	..	..	..	..	..	..	3
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	..	2	..	..	6(6)	..	..	..	8
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	2	..	..	..	..	..	2
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	1(1)	2(2)	1	..	1	..	..	..	5
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	8(1)	9(4)	12(6)	..	..	..	..	..	29
Puerperal Fever	..	..	..	..	..	..	..	..	..
Rubella	..	71(46)	1(1)	..	1	..	..	..	73
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	6	20(9)	7(3)	...	2	..	..	..	35
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	2(1)	..	..	..	2
Trachoma	..	..	..	..	..	..	..	..	..
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	16(9)	18(11)	8(2)	..	5(4)	..	..	..	47
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

[2] Figures not available.

[3] Figures incomplete owing to absence of returns from South Australia.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

O'Sullivan, Brian Francis, M.B., B.S., 1951 (Univ. Sydney), 65 Arden Street, Clovelly, New South Wales.

Farrell, John Campbell, M.B., B.S., 1952 (Univ. Sydney), 14 Yarranabbe Street, Darling Point, New South Wales.

Polla'k, Alexander, registered in accordance with the *Medical Practitioners Act*, 1938-1950, Section 17 (1) (*c*), 247 Old South Head Road, Bondi, New South Wales.

THE undermentioned have been elected as members of the New South Wales Branch of the British Medical Association: Alexander, Ian David (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Ashton Martin, Theone F. (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Barr, Donald Roy (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Berg, Derek Oliver (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Berns, William (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Binks, Robert (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Blackwell, John Bruce (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Boxall, William George (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Brookes, Clifton Walter (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Brooks, John Seymour (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Budd, Graham Murray (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Campbell, Ross (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Cooke, John Montague Baden (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Davis, Geoffrey David (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Faithfull, George Robert (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Farncomb, Ronald John (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Finney, Dallas (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Fischer, Erwin Ludwig (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Flood, William John (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Fuller, Peter Harvey (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Gilchrist, James Gillespie (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Goldberg, David (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Grigor, Wallace Gladstone (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Harden, Peter Alexander (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Hardie, Robert Wilfred (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Hemmings, Ronald Shaw (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Heselton, Thomas William (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Hughes, John Dixon (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Jeffery, Bruce George Ernest (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); King, Keith Laurence (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Korner, Nils Herbert (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Limbers, Paul Apostle (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Loschiavo, Veronica Joan (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Loxton, Ewen Hamilton (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Lyons, Ashwell Lloyd (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); McCallum, Elsie Mae (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); McKinnon, Ian Charles (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); McLeod, John Taylor (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); McLoughlin, Charles George (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Malcolm, Kevin Strathmore (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Marshman, Eric Roy (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Moodie, Peter Martin (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Morgan, Heatherbelle Lucy (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Muntz, Edwin Keith (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Murray, Keith Douglas (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Pfanner, David Walter (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Potts, Lizette Gloria (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Quinn, Thomas Gerald (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Rachow, Elaine Margaret (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Reed, Con Scott Hathaway (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Ringrose, Neville Hall (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Ryan, Clifton John (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Saw, William Anthony Michael (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Smith, John Graham (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Smith, Marion Patricia (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Smith, Norman Dennis John (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Southee, Colin Ethelbert (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Spence, William Allan (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Trenerry, Selwyn Peter (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Whitehouse, John Armson (prov. reg.), M.B., B.S., 1953 (Univ. Sydney); Bassett, Ray, M.B., B.S., 1952 (Univ. Sydney); Church, David Thomas, M.B., B.S., 1952 (Univ. Sydney); Clifton, Bruce Stewart, M.B., B.S., 1952 (Univ. Sydney); Cotton, Keith Lucas, M.B., B.S., 1952 (Univ. Sydney); Garton, David Sydney, M.B., B.S., 1952 (Univ. Sydney); Hughes, Joan Eleanor, M.B., B.S., 1952 (Univ. Sydney); Meredith, John Evan, M.B., B.S., 1952 (Univ. Sydney); Morison, Bruce Dudley, M.B., B.S., 1952 (Univ. Sydney); Morrison, Patrick Thomas, M.B., B.S., 1952 (Univ. Sydney); Nicholas, Judith Nella, M.B., B.S., 1952 (Univ. Sydney); Russell-Jones, Colin Graham, M.B., B.S., 1952 (Univ. Sydney); Bestic, Arthur Edwin, M.B., B.S., 1944 (Univ. Sydney); McDonald, Colin James, M.B., B.S., 1951 (Univ. Sydney); Rose, Herbert Norman, M.B., 1948 (Univ. Sydney); Walsh, Desmond Michael, M.B., B.S., 1951 (Univ. Sydney).

Diary for the Month.

FEB. 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
FEB. 13.—Queensland Branch, B.M.A.: Council Meeting.
FEB. 14.—Tasmanian Branch, B.M.A.: Annual Meeting.
FEB. 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital: all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

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